Title: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Dociparstat Sodium in Combination With Standard Chemotherapy for the Treatment of Newly-Diagnosed Acute Myeloid Leukemia

ClinicalTrials.gov Identifier: NCT04571645

Date: 19 August 2021

TITLE PAGE

Protocol Title: A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of dociparstat sodium in combination with standard chemotherapy for the treatment of newly-diagnosed acute myeloid leukemia

Protocol Number: CMX-DS-003

Compound: Dociparstat sodium (DSTAT; CX-01)

Study Phase: 3

Short Title: Dociparstat in AML with Standard Chemotherapy (**DASH** AML)

Sponsor Name: Chimerix, Inc

Legal Registered Address: 2505 Meridian Parkway, Suite 100; Durham, NC USA 27713

Regulatory Agency Identifier Number(s): US IND 118960

Protocol Version Date: 19 August 2021 (Amendment 2)

Sponsor Signatory: Allen Melemed, Chief Medical Officer

Medical Monitor Name and Contact Information: Refer to the Study Reference Manual

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1. PROTOCOL SYNOPSIS

Name of Sponsor: Chimerix, Inc; 2505 Meridian Parkway, Suite 100; Durham, NC USA 27713	
Name of Investigational Product: dociparstat sodium (DSTAT; CX-01)	
Name of Active Ingredient: 2-O, 3-O desulfated heparin	
Protocol Number: CMX-DS-003 **Version Date**: 19 August 2021 (Amendment 2)	**Phase:** 3
Title of Study: A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of dociparstat sodium in combination with standard chemotherapy for the treatment of newly-diagnosed acute myeloid leukemia **Short Title**: Dociparstat in AML with Standard Chemotherapy (**DASH** AML)	
Regulatory Agency Identifier Number(s): US IND 118960; NCT04571645	
Study Centers: This study will be conducted at approximately 120 centers in the United States, Canada, and other regions (e.g., Australia, Europe) based on feasibility results.	
Number of Participants: Approximately 1000 potential participants are expected to be screened to achieve a total of approximately 570 participants randomly assigned to study intervention.	
Rationale: Dociparstat sodium is a glycosaminoglycan compound derived from porcine heparin that has low anticoagulant activity, but retains the ability to inhibit activities of key proteins implicated in the resistance of acute myeloid leukemia (AML) blasts and leukemic stem cells to chemotherapy (e.g., CXCL12, high mobility group box protein 1 [HMGB1], neutrophil elastase). Dociparstat also inhibits platelet factor 4, which has been demonstrated to play a key role in the maintenance of hematopoietic stem cell quiescence and impairment of platelet recovery after chemotherapy. The current study is being conducted to confirm positive results in previous studies of dociparstat for the treatment of AML and to show the benefits of adding dociparstat to standard 7+3 chemotherapy versus chemotherapy alone for the treatment of newly-diagnosed AML in adults. An open-label pilot study of dociparstat plus standard 7+3 chemotherapy showed positive results in 12 participants with newly-diagnosed AML (NCT02056782). A randomized, controlled, Phase 2b, dose-finding study (NCT02873338) evaluated dociparstat (4 mg/kg intravenous [IV] bolus followed by either 0.125 or 0.25 mg/kg/hr continuous IV infusion for 7 days) in combination with standard 7+3 chemotherapy versus chemotherapy alone in 75 participants ≥60 years of age with newly-diagnosed AML. Results for combined complete remission with complete hematologic recovery (CR) and complete remission with incomplete hematologic recovery (CRi) rates in the dociparstat 0.125 mg/kg/hr and 0.25 mg/kg/hr groups were generally comparable to the chemotherapy alone control group. Observed overall survival (OS) was longer in the dociparstat 0.25 mg/kg/hr group (median not reached [median follow-up for survivors was 20 months]) than the control group (median 11.7 months [95% confidence interval (CI): 7.6, nc]) (observed hazard ratio [HR] 0.68 [95% CI: 0.29, 1.57]). A subset analysis of participants meeting the target inclusion criteria for this Phase 3 study demonstrated a favorable observed HR for dociparstat 0.25 mg/kg/hr (N=20) versus control (N=19) for OS of 0.51. Combination treatment with 7+3 chemotherapy and dociparstat did not show increased toxicity compared with 7+3 chemotherapy alone, nor did it prolong time to platelet or neutrophil recovery.	

Overall Design:

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of dociparstat sodium in combination with standard intensive induction chemotherapy (i.e., cytarabine plus either idarubicin or daunorubicin "7+3" treatment regimen) and cytarabine consolidation chemotherapy versus placebo in combination with standard chemotherapy (i.e., chemotherapy alone) for the treatment of newly-diagnosed AML. This study will enroll approximately 570 adults with de novo AML who are ≥18 years old with intermediate or adverse genetic risk (based on European LeukemiaNet [ELN] 2017 criteria), and who are considered fit for intensive induction chemotherapy.

After completion of all screening evaluations, eligible participants will be randomized by an interactive response technology system in a 1:1 ratio to receive either dociparstat plus standard chemotherapy or placebo plus standard chemotherapy. Randomization will be stratified based upon FMS-like tyrosine kinase 3 (FLT3) status (FLT3-internal tandem duplication [ITD] or tyrosine kinase domain [TKD] positive vs FLT3 mutation negative), genetic risk (intermediate vs adverse), and age (<65 years vs ≥65 years). Of the first 80 participants enrolled, the number of participants between 18 to 59 years of age with intermediate genetic risk will be limited to 20.

Under this protocol, participants will receive an initial induction cycle of 7+3 chemotherapy, a reinduction cycle if bone marrow at Day 14 to 23 shows persistent disease, and up to 4 cycles of consolidation chemotherapy. Treatment response will be assessed by examination of bone marrow aspirates/biopsies and complete blood counts during and at the end of each treatment cycle. After completion (or discontinuation) of protocol treatment, long-term follow-up information will continue to be collected until death or for 5 years after randomization.

The study treatment algorithm is shown in Figure 1. The schedule of activities/assessments is presented in Table 1 for induction cycles and in Table 2 for consolidation cycles.

Note: For the purposes of this study, blinded "study intervention" refers to IV dociparstat or placebo; "standard chemotherapy" and "chemotherapy" refer to the use of cytarabine + anthracycline (either daunorubicin or idarubicin) induction/reinduction therapy, followed by cytarabine consolidation therapy when indicated (although it is recognized that what is standard in one center may not be the same in other regions); "7+3" may specifically refer to the use of 7 days of cytarabine + 3 days of anthracycline for induction therapy, but more generally also includes reinduction and consolidation therapy that follow induction; and "chemotherapy alone" refers to the combination of placebo plus active standard 7+3 chemotherapy. "Induction therapy" is inclusive of the initial induction cycle and a reinduction cycle when applicable.

Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy	
• To compare the efficacy of dociparstat plus standard chemotherapy versus standard chemotherapy alone as upfront treatment for newly-diagnosed AML	• Overall survival (OS).

Objectives	Endpoints
Key Secondary Efficacy	
• To compare the efficacy of dociparstat plus chemotherapy versus chemotherapy alone with respect to event-free survival (EFS).	• EFS following CR. Defined as time from randomization to treatment failure, relapse, or death from any cause, whichever occurs first, with treatment failure defined as failure to achieve CR within 42 days of the start of induction (or start of reinduction, when applicable).
Secondary Efficacy	
• To compare the efficacy of dociparstat plus chemotherapy versus chemotherapy alone with respect to event- and relapse-free survival.	• EFS following CR/CRi, with treatment failure defined as failure to achieve CR/CRi within 42 days of the start of induction (or start of reinduction, when applicable). • Relapse-free survival (RFS) after CR. • RFS after CR/CRi.
To compare measurable residual disease (MRD) status with dociparstat plus chemotherapy versus chemotherapy alone.	• Proportion of participants who achieve CR with MRD_{neg}, as determined by multiparameter (multicolor) flow cytometry (MFC), at the end of induction and consolidation therapy. • Proportion of participants who achieve CR/CRi with MRD_{neg}, as determined by MFC, at the end of induction and consolidation therapy. • Proportion of participants who achieve MRD_{neg} (regardless of CR), as determined by MFC, at the end of induction and consolidation therapy. • Association between CR with MRD_{neg} and relapse. • Association between MRD_{neg} and relapse. • Association between MRD_{neg} and OS.
• To compare post-induction response rates after treatment with dociparstat plus chemotherapy versus chemotherapy alone.	• Proportion of participants who achieve CR. • Proportion of participants who achieve CR/CRi. • Proportion of participants who achieve CR or complete remission with partial hematologic recovery (CRh).
• To compare rates of hematopoietic stem cell transplant (HCT) after treatment with dociparstat plus chemotherapy versus chemotherapy alone.	• Proportion of participants who receive an allogeneic HCT during the study. • Proportion of participants who receive any HCT (allogeneic or autologous) during the study.
• To compare relapse rates after treatment with dociparstat plus chemotherapy versus chemotherapy alone.	• Cumulative incidence of relapse after CR. • Cumulative incidence of relapse after CR/CRi.

• To compare the time to hematologic recovery after induction or reinduction (if indicated) with dociparstat plus chemotherapy versus chemotherapy alone.	• Time to recovery of neutrophil count (absolute neutrophil count [ANC] >500/μL and >1000/μL). • Time to transfusion-independent platelet recovery (>20,000/μL, >50,000/μL, and >100,000/μL). • Incidence of prolonged neutropenia (ANC ≤500/μL past cycle Day 42 in the absence of active leukemia). • Incidence of prolonged thrombocytopenia (platelets ≤50,000/μL past cycle Day 42 in the absence of active leukemia).
• **Other**	
• To evaluate the consistency of dociparstat treatment effects across subgroups.	EFS, OS, and MRD_{neg} across subgroups (e.g., age categories, genetic risk categories).
To evaluate the pharmacokinetic (PK) profile of dociparstat.	Dociparstat PK parameters, including area under the concentration-time curve (AUC), maximum observed concentration (Cmax), time to maximum observed concentration (Tmax), terminal elimination half-life (t½), and clearance, and others as data permit.
• To evaluate the impact of dociparstat on medical resource utilization during induction and consolidation treatment.	• Number of days hospitalized. • Number of days in intensive care unit setting. • Number of blood product (packed red blood cells, platelets) units administered. • Number of growth factor administrations.
• **Safety**	
• To assess the safety and tolerability of dociparstat plus chemotherapy versus chemotherapy alone for the treatment of newly-diagnosed AML.	• Incidence of adverse events (AEs): overall, treatment-related, Grade 3 or higher in severity, serious, fatal, and those resulting in treatment discontinuation. • Incidence of AEs of special interest. • Change from baseline in clinical laboratory parameters. • Distribution of graded clinical laboratory results. • Proportion of participants who meet defined QT/QTc criteria. • Incidence of mortality at Day 30 and Day 60.

Diagnosis and Criteria for Inclusion:

The medical monitor (or designee) will review key entry criteria to confirm eligibility for randomization.

A potential participant must meet **all** the following criteria to be eligible to participate in the study:

1. Newly-diagnosed, previously untreated AML (according to World Health Organization criteria) with at least 20% blasts in the peripheral blood or bone marrow.

2. Age ≥18 years.
   a. Adverse genetic risk (according to ELN criteria), defined as any of the following genetic abnormalities:
      – t(6;9)(p23;q34.1); DEK-NUP214
      – t(v;11q23.3); KMT2A rearranged
      – t(9;22)(q34.1;q11.2); BCR-ABL1
      – inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM(EVI1)
      – -5 or del(5q); -7; -17/abn(17p)
      – Complex karyotype, monosomal karyotype
      – Wild-type NPM1 and FLT3-ITD^{high}
      – Mutated RUNX1, mutated ASXL1, or mutated TP53

      OR

   b. Intermediate genetic risk (according to ELN criteria), defined as any of the following genetic abnormalities:
      – Mutated NPM1 and FLT3-ITD^{high}
      – Wild-type NPM1 without FLT3-ITD or with FLT3-ITD^{low} (without adverse-risk genetic lesions)
      – t(9;11)(p21.3;q23.3); MLLT3-KMT2A
      – Cytogenetic abnormalities not classified as favorable or adverse
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
4. Provide written informed consent to participate in the study.

Criteria for Exclusion:

A potential participant who meets any of the following criteria is **not eligible** to participate in the study:

Leukemia exclusions:

1. Acute promyelocytic leukemia (t(15;17)), myeloid sarcoma without bone marrow involvement, or blast transformation of chronic myelogenous leukemia.
2. Not applicable (criterion removed in Amendment 1).
3. Not applicable (criterion removed in Amendment 1).
4. Clinical evidence of active central nervous system leukemia.

Prior/concomitant therapy:

5. AML treatment, including Vyxeos (CPX-351, liposomal cytarabine and daunorubicin), gemtuzumab ozogamicin, or any other prohibited concomitant AML therapy previously received.
   Note: Prior hydroxyurea and emergency leukapheresis to control white blood cell count are allowed. All-trans retinoic acid during workup and a single dose of intrathecal cytarabine and/or methotrexate is permitted for participants undergoing lumbar puncture to evaluate central nervous system involvement.
6. Receiving any form of anticoagulant therapy (e.g., unfractionated heparin, low molecular weight heparin, coumadin, factor Xa inhibitors).
   Note: Heparin flush of indwelling catheters is permitted.

7. Treatment with any other investigational agent within 28 days or 5 half-lives, whichever is longer, prior to baseline.
8. Any major surgery or radiation therapy within 28 days prior to baseline.

Medical conditions:

9. Immediately life threatening, severe complications of leukemia such as pneumonia with hypoxia or shock, and/or disseminated intravascular coagulation.
10. Active or uncontrolled bleeding at the time of randomization; a bleeding disorder, either inherited or caused by disease; history of known arterial-venous malformation, intracranial hemorrhage, or suspected or known cerebral aneurysm; or clinically significant (in the judgment of the investigator) gastrointestinal bleeding within the 3 weeks prior to randomization.
11. Presence of significant active or uncontrolled infection, including HIV or hepatitis B or C. Note: Patients with an infection receiving treatment (antibiotic, antifungal, or antiviral treatment) may be entered into the study but must be afebrile and hemodynamically stable for ≥72 hours. Patients with current evidence of invasive fungal infection (positive blood or tissue culture) must have subsequent negative cultures to be eligible.
12. Active (uncontrolled, metastatic) second malignancy.
    Note: A second malignancy that is in remission may be permitted if there is clinical evidence of disease stability for a period of greater than 6 months off cytotoxic chemotherapy that is documented by imaging, tumor marker studies, etc. Long-term nonchemotherapy treatment (e.g., hormonal therapy) is acceptable.
13. Psychiatric or neurologic conditions that could compromise participant safety or compliance.
14. History of severe congestive heart failure or other cardiac disease that contraindicates the use of idarubicin or daunorubicin (e.g., cardiac ejection fraction <45%, as determined by echocardiography or multigated acquisition scan).

Diagnostic assessments:

15. QTc >480 msec (see Section 8.3.3 for details about QTc correction formulas).
16. Severe renal impairment, as determined by calculated creatinine clearance <30 mL/min or estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2.
17. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3x upper limit of normal (ULN) or total bilirubin >2x ULN.

Other:

18. Woman of childbearing potential who is pregnant, breastfeeding, and/or not using a highly effective method of contraception (consistent with local regulations regarding the methods of contraception for those participating in clinical studies).
19. History of allergy or hypersensitivity to heparin, pork, or any excipients in the dociparstat formulation.
20. Any other condition, including abnormal laboratory values, that, in the judgement of the investigator, could put the participant at increased risk or interfere with the conduct or planned analyses of the study.

Intervention Groups and Duration: All participants will receive treatment with an initial cycle of standard intensive induction chemotherapy (i.e., cytarabine plus either idarubicin or daunorubicin "7+3" treatment regimen) in combination with randomized study intervention (i.e., dociparstat or placebo). Participants may also receive a reinduction cycle if bone marrow at Day 14 to 23 shows persistent disease, and up to 4 cycles of consolidation chemotherapy. The specific visit schedule and number of cycles of treatment will be dependent on institutional standard practice and each participant's individual response to treatment.

Study intervention dosing is calculated based on weight and chemotherapy dosing is calculated based on body surface area.

	Standard of Care / Background Chemotherapy	**Study Intervention**
Induction cycle – all participants and **Reinduction** cycle (as indicated) – participants 18 to 59 years	All participants will receive an initial induction cycle: • Cytarabine 100 mg/m^2/day via continuous IV infusion 24 hours daily for 7 days (Day 1 to Day 8) **AND** • Anthracycline once daily for 3 days (on Day 1, Day 2, and Day 3): o Idarubicin 12 mg/m^2 by slow (10 to 15 minutes) IV injection **OR** o Daunorubicin 60 mg/m^2 via rapidly flowing IV infusion Note: FLT3-positive participants may receive cytarabine 200 mg/m^2/day. When reinduction is indicated, participants 18 to 59 years will receive the same dosing schedule.	• Dociparstat 4 mg/kg or placebo IV bolus on Day 1, administered 30 minutes after completion of the first dose of idarubicin or daunorubicin, **followed by** • Dociparstat 0.25 mg/kg/hr or placebo by continuous IV infusion for 24 hours daily for 7 days (starting on Day 1 and ending on Day 8 [168 hours])
Reinduction cycle (as indicated) – participants ≥60 years	When reinduction is indicated, participants ≥60 years will receive a modified dosing schedule: • Cytarabine 100 mg/m^2/day via continuous IV infusion for 5 days **AND** • Anthracycline on Day 1 and Day 2: o Idarubicin 12 mg/m^2 by slow (10 to 15 minutes) IV injection **OR** o Daunorubicin 60 mg/m^2 given via rapidly flowing IV infusion Note: FLT3-positive participants may receive cytarabine 200 mg/m^2/day.	• Dociparstat 4 mg/kg or placebo IV bolus on Day 1, administered 30 minutes after completion of the first dose of idarubicin or daunorubicin, **followed by** • Dociparstat 0.25 mg/kg/hr or placebo by continuous IV infusion for 24 hours daily for 5 days (starting on Day 1 and ending on Day 6 [120 hours])

Consolidation cycles (up to 4 cycles, as applicable)	Only participants with a documented response (CR or CRi) are eligible for consolidation. • Cytarabine via IV infusion over 3 hours, administered twice daily (at 12-hour intervals) on Day 1, Day 3, and Day 5 o Age 18-59 years: 3 g/m^2/dose o Age ≥60 years: 1.5 g/m^2/dose	• Dociparstat 4 mg/kg or placebo IV bolus on Day 1, administered 30 minutes after completion of the first dose of cytarabine, **followed by** • Dociparstat 0.25 mg/kg/hr or placebo by continuous IV infusion for 24 hours daily for 5 days (starting on Day 1 and ending on Day 6 [120 hours])

Note: Participants with a FLT3 mutation may also receive treatment with midostaurin at the investigator's discretion and dependent on local availability.

Interruption of Study Intervention:

Infusion of study intervention (i.e., dociparstat or placebo) will be interrupted in the following situations:

aPTT: Participants with activated partial thromboplastin time (aPTT) >45 seconds will have repeat testing performed as soon as practicable. If aPTT is confirmed >45 seconds, interrupt the study intervention infusion. To minimize time that the participant is off therapy, perform repeat testing for aPTT approximately 2 to 6 hours after interruption (as practicable). Infusion may be resumed once aPTT is <35 seconds. Note: samples are not to be obtained from the same line as study intervention infusion (e.g., collect via peripheral venipuncture).

Grade 3 or higher hemorrhagic AEs: Study intervention infusion will be interrupted for Grade 3 or higher hemorrhagic AEs in the setting of aPTT >40 seconds, or Grade 3 or higher hemorrhagic AEs that are deemed to be related to study intervention, regardless of aPTT. Study intervention infusion may be resumed once the participant is determined to be stable and the aPTT is <35 seconds.

Note: Grade 3 or higher hemorrhagic AEs are also considered AEs of special interest.

Renal function: If the calculated creatinine clearance drops below 30 mL/min or eGFR drops below 30 mL/min/1.73 m^2 prior to or during dosing with study intervention, the infusion will be held until the creatinine clearance or eGFR rises to ≥30.

QTc: Study intervention infusion will be interrupted if a participant meets any of the following criteria (based on the average of triplicate electrocardiogram [ECG] readings):

- Without underlying bundle branch block:
  - Interrupt for QTc >500 msec OR uncorrected QT >600 msec
- With underlying bundle branch block:
  - If baseline QTc <450 msec, then interrupt for QTc >500 msec
  - If baseline QTc 450 to 480 msec, then interrupt for QTc >530 msec

In the event of prolonged QTc, the participant should also be assessed for other medications that may impact QT interval, with any necessary changes made to concomitant medications. Infusion of study intervention may be resumed once QTc is <480 msec. Following resumption of infusion, ECGs are to be checked daily until the participant has had 3 consecutive (daily) tracings with QTc <480 msec, after which follow-up ECGs will be as per institutional standard of care.

Bilirubin: If total bilirubin is >2 mg/dL, refer to the daunorubicin/idarubicin product label for dosage adjustments. No adjustment to the study intervention dosing is recommended.

Anticoagulant therapy: If a participant requires short-term anticoagulant therapy, interrupt the administration of study intervention. Infusions may be resumed if anticoagulant therapy is discontinued and aPTT is <35 seconds.

Note: If study intervention is interrupted and not restarted during the same treatment cycle, the participant may receive study intervention (bolus and infusion) during the next treatment cycle (assuming the participant no longer meets any of the interruption criteria).

Criteria for Evaluation

Induction and consolidation treatments are administered as *cycles*. A complete treatment cycle consists of the administration of therapy (i.e., chemotherapy with cytarabine ± anthracycline plus blinded study intervention) and all scheduled assessments to evaluate the response to treatment, including bone marrow and hematologic recovery. The complete duration of a treatment cycle is dependent on the individual participant's response to treatment.

Bone marrow assessments include morphology (cytology), cytogenetics (cell culture and banding analyses), MRD via MFC, and biobanking for future analyses.

Efficacy will be evaluated during and at the end of each treatment cycle. PK will be assessed (at sites with appropriate capabilities) during the initial induction cycle. Safety will be monitored from the time of consent through 42 days after the start of the last treatment cycle (whether or not treatment is completed or discontinued early).

Long-Term Follow-up:

After completion or discontinuation of study intervention, participants will be followed-up until death or for 5 years after randomization. Contact with the participant (or caregiver or treating physician, as applicable) will be made every 3 months for the first 24 months, then every 6 months for the remaining follow-up period. The following information will be collected as applicable: disease status (relapse date), death date, cause of death, and related source documentation. In addition, all AML therapies (i.e., for the treatment of AML and/or prevention of relapse) will be collected from 43 days after start of the last treatment cycle through the time of last study follow-up.

Data Monitoring Committee: Study data will be periodically reviewed by an independent, unblinded, data monitoring committee (DMC). Details of the DMC membership and review procedures will be outlined in a separate charter.

Interim Analysis:

Two interim analyses are planned.

The first interim analysis will be an early unblinded (only to the DMC) assessment of CR, CR with MRD_{neg}, and MRD_{neg}. This analysis will be reviewed by the DMC after 80 evaluable participants complete induction and reinduction (if applicable) assessments. Evaluable participants for this purpose are defined as those who either have a valid MRD result from the induction therapy recovery bone marrow (i.e., Day ~22 to 42), discontinue from induction therapy due to an AE or progressive disease, or die during induction therapy. The study will continue recruitment and enrollment while the interim analyses are being performed; a decision will be made as soon as practicable (targeted within 3 months) after the last participants' last assessments to be included in the analysis.

Three outcomes are possible from this analysis:

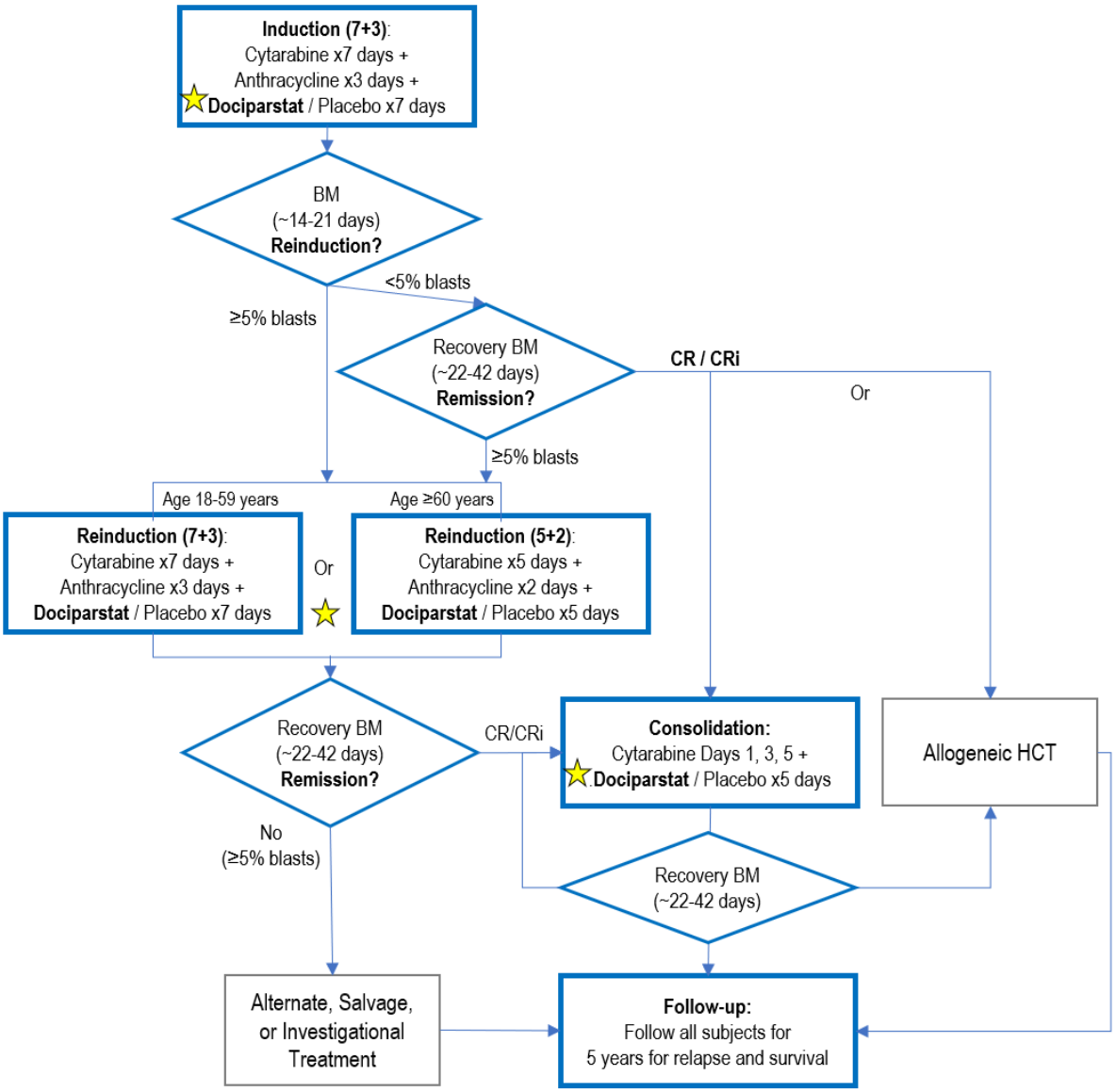
- The observed risk difference for CR is >30%, the observed risk difference for MRD_{neg} is >50%, or the combined total of observed risk differences for CR and CR with MRD_{neg} is >40%. The study will remain blinded and continue as planned.
- Observed risk differences for CR, MRD_{neg}, and CR with MRD_{neg} are all <5%. The study will be unblinded to all parties and stopped.
- Criteria are not met for either of the preceding scenarios. The study will be unblinded to the sponsor, who, in consultation with the United States Food and Drug Administration, will determine whether to continue or stop the study. If the study continues, participants contributing to the interim assessment will not be used in subsequent inferential analyses and will be replaced. A summary of

the data will be shared with investigators and ethics committees and publicly presented. Participants randomized after the interim cutoff and not contributing to the assessment will remain blinded and will contribute to subsequent inferential analyses.

The second interim analysis will be an unblinded (only to the DMC) efficacy assessment. It will be completed after approximately 250 OS events are observed. The O'Brien-Fleming alpha spending function will be used to control the familywise type I error rate. Therefore, the interim OS test will be performed at the 0.0196 nominal two-sided alpha level, and the final OS test will be performed at the 0.0342 nominal two-sided alpha level. On the condition that the study proceeds beyond the first interim analysis, this approach is expected to yield >68% power at the time of this second interim analysis for the primary OS endpoint under the sample size assumptions noted. The key secondary EFS endpoint will also be tested at this time, with the alpha level determined based on the total number of observed EFS events using an alpha spending function that maps to the O'Brien-Fleming boundary. In the event that this interim analysis is successful for either endpoint, the database will be unblinded to the sponsor to facilitate regulatory submissions. Regardless of conclusions from the second interim analysis, participants will continue to be followed as prescribed, with individual group assignments remaining blinded at the site level.

1.1. Study Schema

Figure 1: Treatment Algorithm



Abbreviations: BM=bone marrow aspirate; CR=complete remission; CRi=complete remission with incomplete hematologic recovery; HCT=hematopoietic cell transplant

Notes: The postinduction bone marrow aspirate will be collected on approximately Day 14 to 21.

Participants with a FLT3 mutation may also receive treatment with midostaurin on Days 8 through 21 at the investigator's discretion and dependent on local availability. For these participants, the postinduction bone marrow aspirate will be collected on Day 22 or 23.

Refer to Table 7 for all criteria required to achieve a CR or CRi.

1.2. Schedule of Activities

Table 1: Schedule of Activities/Assessments: Induction Cycle and Reinduction Cycle (as applicable)

Study Day: / Examination / Procedure	Screen [a]	BL/ D1	D 2	D 3	D 4	D 5	D 6	D 7	D 8	D 14-21	D22 until count recovery or Day 42[c]	Post-CR	Early Therapy DC	Notes Study day is relative to start of each treatment cycle
Informed consent	X											Consolidation Therapy, as applicable – see Table 2		
Eligibility criteria	X	X												
Demographics	X													
Medical history	X	X												
ECOG status (induction only)	X	X												
Physical exam and vital signs	X													Predose findings=medical history; Findings after first dose=AE
Height / Weight	X													
ECG (induction only)	X	X							X					D1: Before and after bolus dose; D8: At the end of infusion
Echocardiogram / MUGA scan	X													Repeat per standard of care.
Pregnancy test (as applicable)		X												Women of childbearing potential
Peripheral blood samples:														
– Molecular genetics (central)	X													
– Immunophenotyping (central)	X													
– FISH (central)	X													
– Fibrinogen, D-dimer (local)	X													
– Clinical chemistry (local)	X	X	X		X		X		X	D14			X	
– Hematology (local)	X	X	X		X		X		X	X	X		X	Every other day through recovery.
– PT/INR, aPTT[e,f] (local)	X	X[f]	X	X	X	X	X	X	X	D14			X	Do not draw from the same line used for drug administration[e]
– PK blood samples[e] (central) (induction only) (at sites with appropriate capabilities)		X			X				X					(±10min) D1: predose, end of bolus, and 1 and 12 hours after bolus; D4: morning; D8: end of infusion, and 0.5, 1, 2, and 4 hours after end of infusion
– HMGB1[e,g] (central)		X			X				X	D14	At recovery[b,c]			
– Biobanking (central)	X										X[c]			Optional, per local regulation/approval

Study Day: **Examination / Procedure**	**Screen** [a]	**BL/ D1**	**D 2**	**D 3**	**D 4**	**D 5**	**D 6**	**D 7**	**D 8**	**D 14-21**	**D22 until count recovery or Day 42**[c]	**Post-CR**	**Early Therapy DC**	**Notes** Study day is relative to start of each treatment cycle
Bone marrow aspirate/ biopsy:														
– MRD analyses (central)	X										At recovery[b,c]			Required. Use first draw of marrow.
– Biobanking (central)	X										At recovery[b,c]			Optional, per local regulation/approval
– Morphology (local)	X									X[b]	At recovery[b,c]			
– Cytogenetics (local)	X													
Buccal swab or saliva specimen (central) (induction only)											X			Optional, single sample for germ line analysis
Randomization[a]		X												
Cytarabine – continuous infusion		X	X	X	X	X	X[d]	X[d]						100 mg/m^2/day (Note: FLT3-positive participants may receive 200 mg/m^2/day)
Idarubicin 12 mg/m^2/day OR Daunorubicin 60 mg/m^2/day		X	X	X[d]										
Study intervention – bolus		X												4 mg/kg via IV push, begin 30 min after anthracycline infusion ends
Study intervention – continuous infusion		X	X	X	X	X	X[d]	X[d]						0.25 mg/kg/hour; Begin after bolus dose
Adverse event assessments	Procedure-related SAEs	All AEs ----------→											X	Record through 42 days after start of the last induction or consolidation treatment cycle (regardless of completion or discontinuation)
Concomitant medications	X	----------→											X	
Medical resource utilization		----------→											X	

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; CR=complete response; D=day; D14=Day 14 (only day specified within window); DC=discontinuation; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; FISH=fluorescence in situ hybridization; HMGB1=high mobility group box protein 1; MRD=measurable residual disease; MUGA=multigated acquisition scan; PK=pharmacokinetics; PT/INR=prothrombin time/international normalized ratio; SAE=serious adverse event

Refer to footnotes on the next page

[a] All prestudy/screening procedures (including cytogenetic and molecular analyses) will ideally be completed within 14 days of randomization. First dose of study intervention should be administered as soon as possible after randomization, and must be administered no more than 24 hours after randomization. Screening procedures do not need to be repeated prior to reinduction.

[b] Bone marrow aspirate/biopsy will be performed once between approximately Day 14 and Day 21 (Day 22-23 for participants taking midostaurin), when peripheral blood is negative for persistent AML, to determine the need for reinduction. (If the ~Day 14 bone marrow is not evaluable or assessment of aplasia is equivocal, a repeat evaluation may be performed 5 to 14 days later, at the discretion of the investigator, in order to determine effect and need for second induction). Thereafter, additional bone marrow samples will be collected to confirm response/persistence/relapse after second induction and consolidation cycles. For participants who achieve CR/CRi, measurable residual disease assays will be performed by the central laboratory on the recovery marrow sample.

[c] Count recovery is defined as an absolute neutrophil count >1000/µL and a platelet count >100,000/µL. If count recovery occurs, perform bone marrow aspirate/biopsy within 7 days. If count recovery has not occurred by ~Day 36 after induction or reinduction, perform a bone marrow aspirate/biopsy on or before Day 42 to evaluate disease status.

[d] Participants who do not achieve leukemia-free state (<5% bone marrow blasts) on bone marrow aspirate performed between ~Days 14-21 (Day 22-23 for participants taking midostaurin) may receive a reinduction cycle. Participants 18 to 59 years will receive the same 7+3 regimen; participants ≥60 years will receive a modified "5+2" regimen, with cytarabine and study intervention administered on Days 1 through 5 and idarubicin/daunorubicin on Days 1 and 2.

[e] Do not draw blood (especially for aPTT or PK analyses) from the same line that is used for study intervention administration. Drawing blood from a heparinized line may falsely alter results obtained; if using an indwelling catheter, draw ~5 mL of blood from the line for discard before drawing the aPTT and PK samples.

[f] Draw blood for aPTT measurements no sooner than 8 hours after the bolus dose. During the continuous infusion, measure aPTT daily.

[g] Refer to laboratory manual for instructions on obtaining a separate sample for HMGB1 analyses versus using a biobanked sample.

Note: All participants will be followed-up for long-term outcomes for 5 years after randomization. See Section 8.2.3.

Table 2: Schedule of Activities/Assessments: Consolidation Cycles

Study Day: Examination / Procedure	D1	D2	D3	D4	D5	D6	D14	D7 until count recovery or D42[h]	Follow-up	Notes
										Day is relative to start of each treatment cycle
Weight	X								Monitor remission status via blood counts and bone marrow aspirates per institutional standard of care; Long-term study follow-up is 5 years[k]	
Bone marrow aspirate/ biopsy:										After each consolidation cycle and to confirm response/ relapse/ persistent disease
–Morphology (local)								X – at recovery		
–MRD analyses (central)								X – at recovery		After each consolidation cycle
–Biobanking (central)								X – at recovery		Optional, per local regulations/approvals
Peripheral blood samples:										
–Hematology (local)	X	X		X		X	X	X		Every other day through recovery
–Clinical chemistry (local)	X	X		X		X	X			
–PT/INR, aPTT[i,j] (local)	X	X	X	X	X	X	X			
–HMGB1 [g,i] (central)	X							X – at recovery		
–Biobanking (central)								X – at recovery		
Cytarabine – Infusion over 3 hours, twice daily	X		X		X					18 to 59 years: 3 g/m^2/dose; ≥60 years: 1.5 g/m^2/dose
Study intervention – bolus	X									4 mg/kg via IV push over 5 minutes, begin 30 minutes after cytarabine infusion ends
Study intervention – continuous infusion	X	X	X	X	X					0.25 mg/kg/hour. Begin after bolus dose
Adverse event assessments	----------→									Record through 42 days after the start of last cycle (regardless of completion or discontinuation)
Concomitant medications	----------→									
Medical resource utilization	----------→									

Abbreviations: aPTT=activated partial thromboplastin time; CR=complete response; D=day; HMGB1=high mobility group box protein 1; MRD=measurable residual disease; PT/INR=prothrombin time/international normalized ratio

[g] Refer to laboratory manual for instructions on obtaining a separate sample for HMGB1 analyses versus using a biobanked sample. Only samples from the last consolidation cycle will be analyzed.

[h] Count recovery is defined as an absolute neutrophil count >1000/µL and a platelet count >100,000/µL. If count recovery has not occurred by ~Day 36, perform a bone marrow aspirate/biopsy on or before Day 42 to evaluate disease status.

[i] Do not draw blood (especially for aPTT analyses) from the same line that is used for study intervention administration. Drawing blood from a heparinized line may falsely alter results obtained; therefore, if using an indwelling catheter, draw approximately 5 mL of blood from the line for discard before drawing the sample for analysis.

[j] Draw blood for aPTT measurements no sooner than 8 hours after the bolus dose. During the continuous infusion, measure aPTT daily.

[k] All participants will be followed-up for long-term outcomes for 5 years after randomization. See Section 8.2.3.

2. INTRODUCTION

Dociparstat sodium is being developed for the treatment of newly-diagnosed acute myeloid leukemia (AML) in combination with standard chemotherapy in adults.

2.1. Study Rationale

The addition of dociparstat to standard 7+3 chemotherapy is expected to improve overall survival (OS) and relapse-free survival (RFS) versus chemotherapy alone, without additive toxicity. The current study is being conducted to confirm positive efficacy and safety results in previous studies of dociparstat for the treatment of AML and to show the benefits of adding dociparstat to standard 7+3 chemotherapy versus chemotherapy alone for the treatment of newly-diagnosed AML in adults.

2.2. Background

AML is the most common type of acute leukemia in adults, with a median age of onset of 68 years and an increasing risk of significant morbidity and mortality with increasing age. In patients suitable for intensive treatment, the standard of care for newly-diagnosed AML remains cytarabine and an anthracycline in a 7+3 induction regimen. This combination has been used for more than 40 years and there remains an unmet medical need to increase the efficacy of treatment by preventing or delaying relapse and improving survival, and to accomplish this goal without additive toxicity.

Dociparstat sodium is a glycosaminoglycan compound derived from porcine heparin that has low anticoagulant activity, but retains the ability to inhibit activities of key proteins implicated in the resistance of AML blasts and leukemic stem cells to chemotherapy (e.g., CXCL12, high mobility group box protein 1 [HMGB1], neutrophil elastase) (Rao 2010; Ziarek 2013; Zhang 2012). Dociparstat also inhibits platelet factor 4, which has been demonstrated to play a key role in the maintenance of hematopoietic stem cell quiescence and impairment of platelet recovery after chemotherapy (Tkaczynski 2018; Lambert 2007; Lambert 2012). Inhibition of these key proteins by dociparstat may result in sensitization of low abundance resistant AML blasts and quiescent leukemic stem cells, leading to deeper and more durable responses to cell cycle-dependent chemotherapies.

This multimodal mechanism of action would be particularly beneficial in a disease with significant heterogeneity like AML, and may provide an advantage relative to other therapies with singular targets (e.g., CXCR4 inhibitors, E-selectin inhibitors).

An open-label pilot study of dociparstat plus standard 7+3 chemotherapy showed positive results in 12 participants with newly-diagnosed AML (NCT02056782) (Kovacsovics 2018). Three participants were classified as having good risk, 5 had intermediate risk, and 4 had poor-risk disease characteristics. Eleven participants (92%) had morphologic complete remission (CR) after the initial induction cycle. Eight participants were alive at a median follow-up of 24 months (4 participants in CR). Three participants received an allogeneic stem cell transplant after the initial induction cycle. Median disease-free survival was 14.8 months; median OS was not attained at the maximum follow-up time of 29.4 months.

A randomized, controlled, Phase 2b, dose-finding study (NCT02873338) evaluated dociparstat (4 mg/kg intravenous [IV] bolus followed by either 0.125 or 0.25 mg/kg/hr continuous IV infusion for 7 days) in combination with standard 7+3 chemotherapy versus chemotherapy alone in 75 participants ≥60 years of age with newly-diagnosed AML. Results for combined complete remission with complete hematologic recovery (CR) and complete remission with incomplete hematologic recovery (CRi) rates in the dociparstat 0.125 mg/kg/hr and 0.25 mg/kg/hr groups were generally comparable to the chemotherapy alone control group. Observed OS was longer in the dociparstat 0.25 mg/kg/hr group (median not reached [median follow-up for survivors was 20 months]) than the control group (median 11.7 months [95% confidence interval (CI): 7.6, nc]) (observed hazard ratio [HR] 0.68 [95% CI: 0.29, 1.57]). A subset analysis of participants meeting the target inclusion criteria for this Phase 3 study demonstrated a favorable observed HR for dociparstat 0.25 mg/kg/hr (N=20) versus control (N=19) for OS of 0.51. Combination treatment with 7+3 chemotherapy and dociparstat did not show increased toxicity compared with 7+3 chemotherapy alone, nor did it prolong time to platelet or neutrophil recovery. Febrile neutropenia was reported as a severe adverse event (AE) more commonly for participants in the dociparstat 0.25 mg/kg/hr group (n=3) than control (n=1); the incidence of infections, however, was comparable. The activated partial thromboplastin time (aPTT) remained within the normal range for most participants in both the dociparstat and control groups; there was no excess in hemorrhagic AEs in participants treated with dociparstat 0.25 mg/kg/hr.

A detailed description of the chemistry, pharmacology, efficacy, and safety of dociparstat is provided in the investigator's brochure.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits, risks, and reasonably expected AEs of dociparstat may be found in the investigator's brochure. Refer to the approved product labeling for detailed information about the known and expected risks of cytarabine, daunorubicin, and idarubicin.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Study Intervention: Dociparstat		
Bleeding and hemorrhagic AEs	Based on results of nonclinical and clinical studies and the relationship of dociparstat to heparin (refer to data in the investigator's brochure).	Inclusion/exclusion criteria and screening assessments are designed to limit enrollment to participants who are less likely to have confounding conditions that could impact their safety (see Section 5). Participants will be routinely monitored throughout the infusion period. Dosing will be interrupted for prolonged aPTT or hemorrhagic AEs Grade 3 or higher (see Section 7).

Potential Risk of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Study Procedures		
Pain, bleeding, and infection at site of bone marrow aspiration.	These are known risks of the procedure, which will be performed multiple times during the study.	Bone marrow aspiration/biopsy procedures are only to be performed by qualified medical personnel. Participants will receive treatment for any adverse effects.
Other		
Myelosuppression	Cytarabine reduces blood cell production in the marrow. Increased risk of bleeding and infections.	Blood counts will be routinely monitored during treatment and until hematologic recovery. Site personnel and study participants will use infection prophylaxis practices and report the first sign/symptom of infection.
Cardiotoxicity (severe congestive heart failure)	Anthracyclines have been associated with a risk of cardiotoxicity.	Inclusion/exclusion criteria and screening assessments are designed to prevent enrollment of participants with preexisting cardiac dysfunction (see Section 5). The cumulative anthracycline dose in this study is below the threshold for increased risk, as specified in the product labels.
Severe local tissue necrosis	Extravasation during anthracycline administration has been associated with tissue necrosis	Must be given into a rapidly flowing intravenous infusion.

2.3.2. Benefit Assessment

Treatment with dociparstat in combination with standard 7+3 chemotherapy may result in reduced risk for relapse and longer survival than treatment with standard chemotherapy alone.

The cytogenetic, molecular, and MRD analyses performed during this study may provide additional prognostic information that may influence future treatment decisions.

AML is a rare condition and an area of unmet need for successful treatments; participants in this study will contribute to the process of developing a potential new therapeutic treatment option and expanding general knowledge about AML treatment.

2.3.3. Overall Benefit: Risk Conclusion

AML is a serious, life-threatening condition with limited options for successful treatment.

Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with dociparstat represent a minimal increase in risk of treatment versus standard chemotherapy alone. The use of dociparstat is justified by the anticipated benefits that may be afforded to participants with AML in this study.

3. OBJECTIVES AND ENDPOINTS

For definitions and response and outcomes criteria, refer to Section 8.2.2 and Appendix 7.

Objectives	Endpoints
Primary Efficacy	
• To compare the efficacy of dociparstat plus standard chemotherapy versus standard chemotherapy alone as upfront treatment for newly-diagnosed AML	• Overall survival (OS).
Key Secondary Efficacy	
• To compare the efficacy of dociparstat plus chemotherapy versus chemotherapy alone with respect to event-free survival (EFS).	• EFS following CR. Defined as time from randomization to treatment failure, relapse, or death from any cause, whichever occurs first, with treatment failure defined as failure to achieve CR within 42 days of the start of induction (or start of reinduction, when applicable).
Secondary Efficacy	
• To compare the efficacy of dociparstat plus chemotherapy versus chemotherapy alone with respect to event- and relapse-free survival.	• EFS following CR/CRi, with treatment failure defined as failure to achieve CR/CRi within 42 days of the start of induction (or start of reinduction, when applicable). • Relapse-free survival (RFS) after CR. • RFS after CR/CRi.
• To compare MRD status with dociparstat plus chemotherapy versus chemotherapy alone.	• Proportion of participants who achieve CR with MRD_{neg}, as determined by multiparameter (multicolor) flow cytometry (MFC), at the end of induction and consolidation therapy. • Proportion of participants who achieve CR/CRi with MRD_{neg}, as determined by MFC, at the end of induction and consolidation therapy. • Proportion of participants who achieve MRD_{neg} (regardless of CR), as determined by MFC, at the end of induction and consolidation therapy. • Association between CR with MRD_{neg} and relapse. • Association between MRD_{neg} and relapse. • Association between MRD_{neg} and OS.
• To compare post-induction response rates after treatment with dociparstat plus chemotherapy versus chemotherapy alone.	• Proportion of participants who achieve CR. • Proportion of participants who achieve CR/CRi. • Proportion of participants who achieve CR or complete remission with partial hematologic recovery (CRh).

Objectives	Endpoints
• To compare rates of hematopoietic stem cell transplant (HCT) after treatment with dociparstat plus chemotherapy versus chemotherapy alone.	• Proportion of participants who receive an allogeneic HCT during the study. • Proportion of participants who receive any HCT (allogeneic or autologous) during the study.
• To compare relapse rates after treatment with dociparstat plus chemotherapy versus chemotherapy alone.	• Cumulative incidence of relapse after CR. • Cumulative incidence of relapse after CR/CRi.
• To compare the time to hematologic recovery after induction or reinduction (if indicated) with dociparstat plus chemotherapy versus chemotherapy alone.	• Time to recovery of neutrophil count (ANC >500/μL and >1000/μL). • Time to transfusion-independent platelet recovery (>20,000/μL, >50,000/μL, and >100,000/μL). • Incidence of prolonged neutropenia (ANC ≤500/μL past cycle Day 42 in the absence of active leukemia). • Incidence of prolonged thrombocytopenia (platelets ≤50,000/μL past cycle Day 42 in the absence of active leukemia).
Other	
• To evaluate the consistency of dociparstat treatment effects across subgroups.	• EFS, OS, and MRD_{neg} across subgroups (e.g., age categories, genetic risk categories).
• To evaluate the pharmacokinetic (PK) profile of dociparstat.	• Dociparstat PK parameters, including area under the concentration-time curve (AUC), maximum observed concentration (C_{max}), time to maximum observed concentration (T_{max}), terminal elimination half-life ($t_{½}$), and clearance, and others as data permit.
• To evaluate the impact of dociparstat on medical resource utilization during induction and consolidation treatment.	• Number of days hospitalized. • Number of days in intensive care unit setting. • Number of blood product (packed red blood cells, platelets) units administered. • Number of growth factor administrations.
Safety	
• To assess the safety and tolerability of dociparstat plus chemotherapy versus chemotherapy alone for the treatment of newly-diagnosed AML.	• Incidence of AEs: overall, treatment-related, Grade 3 or higher in severity, serious, fatal, and those resulting in treatment discontinuation. • Incidence of AEs of special interest. • Change from baseline in clinical laboratory parameters. • Distribution of graded clinical laboratory results. • Proportion of participants who meet defined QT/QTc criteria. • Incidence of mortality at Day 30 and Day 60.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of dociparstat sodium in combination with standard intensive induction chemotherapy (i.e., cytarabine plus either idarubicin or daunorubicin "7+3" treatment regimen) and cytarabine consolidation chemotherapy versus placebo in combination with standard chemotherapy (i.e., chemotherapy alone) for the treatment of newly-diagnosed AML. This study will enroll approximately 570 adults with de novo AML who are ≥18 years old with intermediate or adverse genetic risk (based on European LeukemiaNet [ELN] 2017 criteria; see Appendix 4), and who are considered fit for intensive induction chemotherapy.

After completion of all screening evaluations, eligible participants will be randomized by an interactive response technology (IRT) system in a 1:1 ratio to receive either dociparstat plus standard chemotherapy or placebo plus standard chemotherapy. Randomization will be stratified based upon FMS-like tyrosine kinase 3 (FLT3) status (FLT3-internal tandem duplication [ITD] or tyrosine kinase domain [TKD] positive vs FLT3 mutation negative), genetic risk (intermediate vs adverse), and age (<65 years vs ≥65 years). Of the first 80 participants enrolled, the number of participants between 18 to 59 years of age with intermediate genetic risk will be limited to 20.

Under this protocol, participants will receive an initial induction cycle of 7+3 chemotherapy, a reinduction cycle if bone marrow at Day 14 to 23 shows persistent disease, and up to 4 cycles of consolidation chemotherapy. Treatment response will be assessed by examination of bone marrow aspirates/biopsies and complete blood counts during and at the end of each treatment cycle. After completion (or discontinuation) of protocol treatment, long-term follow-up information (e.g., date of HCT if performed, AML therapies received, date of disease relapse/recurrence [including results of tests used for diagnosis of recurrence], and vital status) will continue to be collected (via medical records and/or phone/email contact with the study center) until death or for 5 years after randomization.

For definitions, response and outcomes criteria, and abbreviations used in this protocol, refer to Appendix 7 and Appendix 8.

4.2. Scientific Rationale for Study Design

A randomized, double-blind, placebo-controlled study design was selected as the most robust design to minimize potential bias.

Adults with newly-diagnosed, previously-untreated AML, who are fit for intensive, potentially curative, chemotherapy (and who do not meet any of the exclusion criteria) will be eligible for enrollment. This study is focused on the treatment of participants with intermediate or adverse genetic risk because the need for more effective treatment options is greater in this population than in patients with favorable risk (NCCN 2019).

The American Society of Hematology 2020 guidelines for treating newly-diagnosed AML in older adults recommends offering antileukemic therapy (if a candidate for such therapy) over best supportive care only and suggests intensive antileukemic therapy (if considered fit for intensive therapy) over less-intensive therapy; the panel also suggests postremission therapy (if not a candidate for HCT) over no additional therapy (Sekeres 2020). Consistent with these

guidelines the investigator is advised to discuss all options with each potential participant (especially older adults) to understand their treatment goals and reach an agreement on the choice of pursuing antileukemic treatment with intensive combination therapy and postremission consolidation therapy as applicable.

During initial induction therapy, all participants will receive background treatment with the current standard of care, 7+3 regimen of cytarabine + anthracycline chemotherapy; therefore, all participants will be actively treated for AML while preserving the ability to identify an additional treatment effect from the study intervention (dociparstat versus placebo). Chemotherapy dosing was selected to align with NCCN guidelines (NCCN 2019).

The goal of induction therapy is to clear leukemia, leading to clinical remission, and ultimately longer survival; therefore, the primary endpoint is OS, defined as the time from randomization to death from any cause. EFS is a clinically-relevant, key secondary endpoint that is expected to show a differential treatment benefit for dociparstat plus 7+3 chemotherapy versus chemotherapy alone. Despite high rates of remission, more than 50% of adult AML patients relapse after attaining morphological CR after induction therapy. MRD_{neg} status at the end of induction/consolidation therapy is correlated with improved OS, and may ultimately serve as a more independent measure of the activity of up-front chemotherapy than long-term measures (e.g., OS and EFS), given the potential confounding effects of HCT and other maintenance and salvage therapies on those outcomes. Therefore, negative MRD status after treatment is an important secondary endpoint and will be used as a factor in the early interim analysis of efficacy.

4.3. Justification for Dose

Dociparstat will be administered as an IV bolus dose of 4 mg/kg on Day 1, followed by a continuous IV infusion of 0.25 mg/kg/hr for 7 days during standard 7+3 induction chemotherapy. Selection of the dose of dociparstat for the treatment of AML was based upon the dual requirements to achieve a high enough drug concentration to be effective while also minimizing the potential for adverse effects related to prolongation of coagulation time.

In an AML pilot study, this combination of dociparstat dosing (i.e., 4 mg/kg bolus plus 0.25 mg/kg/hr continuous infusion) added on to the standard 7+3 chemotherapy regimen of cytarabine and idarubicin, resulted in 11 of 12 participants (92%) achieving a complete bone marrow response after a single induction cycle. Dociparstat did not increase the risk of bleeding; anti-factor Xa activity was not significantly changed from baseline and remained below published therapeutic anticoagulant reference ranges.

The randomized Phase 2b AML study also included a fixed bolus dose of 4 mg/kg dociparstat, but initially included 3 dose levels (0.125, 0.25, and 0.325 mg/kg/hr) for the continuous infusion. The 0.325 mg/kg/hr dose level was discontinued after 1 of 2 participants dosed experienced a fatal serious adverse event (SAE) of retroperitoneal hemorrhage and a contributory role of dociparstat could not be excluded. During dociparstat 0.25 mg/kg/hr infusion, aPTT levels were numerically higher than the 0.125 mg/kg/hr or control groups, but generally remained in the normal range. There was no excess of bleeding AEs for dociparstat 0.25 mg/kg/hr versus control. The overall safety profile was similar for the 0.125 and 0.25 mg/kg/hr dose groups, but efficacy was greater for the 0.25 mg/kg/hr group.

This Phase 3 study will administer dociparstat as an IV bolus dose of 4 mg/kg, followed by a continuous IV infusion of 0.25 mg/kg/hr. All participants will receive an initial induction cycle. A second induction cycle (reinduction) is recommended for participants with a reduction in leukemia burden, but persistent blast counts ≥5% on the initial bone marrow assessment (~Day 14 to 21, or Day 22 to 23 for participants taking midostaurin; or the initial response assessment at approximately Day 22 to 42 after initial induction). The original 7+3 schedule will be utilized for reinduction in participants <60 years; a modified 5+2 dosing schedule will be utilized for reinduction in participants ≥60 years of age.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the long-term follow-up.

The end of the study is defined as the date of the last visit (or last follow-up contact) of the last participant in the study globally.

5. STUDY POPULATION

The target study population is adults with de novo AML who are ≥18 years old with intermediate or adverse genetic risk (based on ELN 2017 criteria; see Appendix 4), and who are considered fit for intensive induction chemotherapy. The investigator is advised to discuss all options with each potential participant (especially older adults) to reach an agreement on the choice of pursuing antileukemic treatment (versus supportive management only) with intensive combination therapy and postremission consolidation therapy as applicable.

The medical monitor (or designee) will review key entry criteria to confirm eligibility for randomization. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

A potential participant must meet **all** the following criteria to be included in the study:

1. Newly-diagnosed, previously untreated AML (according to World Health Organization criteria) with at least 20% blasts in the peripheral blood or bone marrow.
2. Age ≥18 years.
   a. Adverse genetic risk (according to ELN criteria), defined as any of the following genetic abnormalities:
      – t(6;9)(p23;q34.1); DEK-NUP214
      – t(v;11q23.3); KMT2A rearranged
      – t(9;22)(q34.1;q11.2); BCR-ABL1
      – inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM(EVI1)
      – -5 or del(5q); -7; -17/abn(17p)
      – Complex karyotype, monosomal karyotype
      – Wild-type NPM1 and FLT3-ITD^{high}
      – Mutated RUNX1, mutated ASXL1, or mutated TP53

      OR

   b. Intermediate genetic risk (according to ELN criteria), defined as any of the following genetic abnormalities:
      – Mutated NPM1 and FLT3-ITD^{high}
      – Wild-type NPM1 without FLT3-ITD or with FLT3-ITD^{low} (without adverse-risk genetic lesions)
      – t(9;11)(p21.3;q23.3); MLLT3-KMT2A
      – Cytogenetic abnormalities not classified as favorable or adverse
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
4. Provide written informed consent to participate in the study.

5.2. Exclusion Criteria

A potential participant will be excluded from the study if **any** of the following criteria apply:

Leukemia exclusions:

1. Acute promyelocytic leukemia (t(15;17)), myeloid sarcoma without bone marrow involvement, or blast transformation of chronic myelogenous leukemia.
2. Not applicable (criterion removed in Amendment 1).
3. Not applicable (criterion removed in Amendment 1).
4. Clinical evidence of active central nervous system leukemia.

Prior/concomitant therapy:

5. AML treatment, including Vyxeos (CPX-351, liposomal cytarabine and daunorubicin), gemtuzumab ozogamicin, or any other prohibited concomitant AML therapy previously received or anticipated to start during the study.
   Note: Prior hydroxyurea and emergency leukapheresis to control white blood cell count are allowed. All-trans retinoic acid during workup and a single dose of intrathecal cytarabine and/or methotrexate is permitted for participants undergoing lumbar puncture to evaluate central nervous system involvement.
6. Receiving any form of anticoagulant therapy (e.g., unfractionated heparin, low molecular weight heparin, coumadin, factor Xa inhibitors).
   Note: Heparin flush of indwelling catheters is permitted.
7. Treatment with any other investigational agent within 28 days, or 5 half-lives, whichever is longer, prior to baseline.
8. Any major surgery or radiation therapy within 28 days prior to baseline.

Medical conditions:

9. Immediately life threatening, severe complications of leukemia such as pneumonia with hypoxia or shock, and/or disseminated intravascular coagulation
10. Active or uncontrolled bleeding at the time of randomization; a bleeding disorder, either inherited or caused by disease; history of known arterial-venous malformation, intracranial hemorrhage, or suspected or known cerebral aneurysm; or clinically significant (in the judgment of the investigator) gastrointestinal bleeding within the 3 weeks prior to randomization.
11. Presence of significant active or uncontrolled infection, including HIV or hepatitis B or C. Note: Patients with an infection receiving treatment (antibiotic, antifungal, or antiviral treatment) may be entered into the study but must be afebrile and hemodynamically stable for ≥72 hours. Patients with current evidence of invasive fungal infection (positive blood or tissue culture) must have subsequent negative cultures to be eligible.
12. Active (uncontrolled, metastatic) second malignancy.
    Note: A second malignancy that is in remission may be permitted if there is clinical evidence of disease stability for a period of greater than 6 months off cytotoxic

chemotherapy that is documented by imaging, tumor marker studies, etc. Long-term nonchemotherapy treatment (e.g., hormonal therapy) is acceptable.

13. Psychiatric or neurologic conditions that could compromise participant safety or compliance.
14. History of severe congestive heart failure or other cardiac disease that contraindicates the use of idarubicin or daunorubicin (e.g., cardiac ejection fraction <45%, as determined by echocardiography or multigated acquisition scan).

Diagnostic assessments:

15. QTc >480 msec (see Section 8.3.3 for details about QTc correction formulas).
16. Severe renal impairment, as determined by calculated creatinine clearance <30 mL/min or estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2.
17. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3x upper limit of normal (ULN) or total bilirubin >2x ULN.

Other:

18. Woman of childbearing potential who is pregnant, breastfeeding, and/or not using a highly effective method of contraception (consistent with local regulations regarding the methods of contraception for those participating in clinical studies). Refer to Appendix 3 for guidance.
19. History of allergy or hypersensitivity to heparin, pork, or any excipients in the dociparstat formulation.
20. Any other condition, including abnormal laboratory values, that, in the judgment of the investigator, could put the participant at increased risk or interfere with the conduct or planned analyses of the study.

5.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, reason(s) for screen failure, eligibility criteria, and any study-procedure related SAEs.

Individuals whose ALT, AST, bilirubin, creatinine clearance, or eGFR results initially do not meet the criteria for participation in this study may have the test(s) repeated one time within 10 days; if the repeat value is not exclusionary, the participant may be eligible for enrollment and randomization.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention, marketed products, or placebo intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Induction and consolidation treatments are administered as *cycles*. A complete treatment cycle consists of the administration of therapy (i.e., chemotherapy with cytarabine ± anthracycline plus blinded study intervention) and all scheduled assessments to evaluate the response to treatment, including bone marrow and hematologic recovery.

Details of dociparstat solution for injection are listed in Table 3 and standard of care chemotherapy agents are listed in Table 4. Details of the dosing regimens for each treatment cycle (and age group) are presented in Table 5.

Table 3: Dociparstat Details

Intervention Name	Dociparstat sodium
Type	Drug
Dose Formulation	Solution for injection
Unit Dose Strength(s)	50 mg/mL
Route of Administration	Intravenous infusion (bolus followed by continuous infusion)
Use	Experimental agent
IMP or Non-IMP	Investigational medicinal product (IMP)
Sourcing	Provided centrally by the sponsor
Packaging and Labeling	Provided in 10-mL vials (1 vial per kit). Each kit and vial will be labeled in accordance with applicable regulatory requirements.
Current/ Former Names	Dociparstat sodium; 2-O, 3-O desulfated heparin; ODSH; DSTAT; CX-01

Normal saline (sodium chloride 0.9%) will be used to dilute dociparstat solution for injection before each infusion. In order to maintain blinding of randomized study intervention, normal saline will also be used as the de facto placebo. Commercially-available product will be purchased and provided (sourced) locally by the study site (or subsidiary or designee); packaging and labeling will be per local requirements for commercial products.

Table 4: Standard of Care Therapy Details

Group Name	**Standard of Care for the Dociparstat and Placebo Groups** (cytarabine + an anthracycline will be administered to all participants)		
Intervention Name	Cytarabine	Idarubicin[a]	Daunorubicin[a]
Type	Drug	Drug	Drug
Dose Formulation	Solution for injection		
Unit Dose Strength(s)	Refer to product label		
Route of Administration	IV infusion		
Use	Standard of care chemotherapy		
IMP or Non-IMP	Non-investigational medicinal product (NIMP)		
Sourcing	Provided locally by the study site, subsidiary, or designee		
Packaging and Labeling	Commercial product packaging and labeling		
Current/ Former Names [b]	Ara-C, DepoCyt, cytosine arabinoside, cytarbel, Cytosar, aracytidine, Aracytin, arabine, 1-beta-d-arabinofuranosylcytosine	Idamycin, Idaru, Zavedos	Cerubidine, daunomycin, rubidomycin, rubomycin C, daunorrubicina leukaemomycin C

[a] The use of idarubicin versus daunorubicin is at the discretion of the investigator based on standard institutional practice.
[b] List is not exhaustive of all product names available in all countries.

Dociparstat sodium solution for injection is supplied as 1-vial kits. Calculate dosing based on participant weight and prepare/dilute the drug product before IV infusion. Dociparstat must be administered via a dedicated infusion line. Do not mix with other IV medications.

Dociparstat is administered as an initial IV bolus dose over 5 minutes, immediately followed by a continuous IV infusion 24 hours daily for 5 or 7 days (see Table 5). Dociparstat is intended for use in combination with standard chemotherapy (i.e., dociparstat should not be used as monotherapy).

Table 5: Dosing Regimen for Induction and Consolidation Therapy

	Standard of Care / Background Chemotherapy	**Study Intervention**
Induction cycle – all participants and **Reinduction** cycle (as indicated) – participants 18 to 59 years	All participants will receive an initial induction cycle: • Cytarabine 100 mg/m^2/day via continuous IV infusion 24 hours daily for 7 days (Day 1 to Day 8) **AND** • Anthracycline once daily for 3 days (on Day 1, Day 2, and Day 3): o Idarubicin 12 mg/m^2 by slow (10 to 15 minutes) IV injection **OR** o Daunorubicin 60 mg/m^2 via rapidly flowing IV infusion Note: FLT3-positive participants may receive cytarabine 200 mg/m^2/day. When reinduction is indicated, participants 18 to 59 years will receive the same dosing schedule.	• Dociparstat 4 mg/kg or placebo IV bolus on Day 1, administered 30 minutes after completion of the first dose of idarubicin or daunorubicin, **followed by** • Dociparstat 0.25 mg/kg/hr or placebo by continuous IV infusion for 24 hours daily for 7 days (starting on Day 1 and ending on Day 8 [168 hours])
Reinduction cycle (as indicated) – participants ≥60 years	When reinduction is indicated, participants ≥60 years will receive a modified dosing schedule: • Cytarabine 100 mg/m^2/day via continuous IV infusion for 5 days **AND** • Anthracycline on Day 1 and Day 2: o Idarubicin 12 mg/m^2 by slow (10 to 15 minutes) IV injection **OR** o Daunorubicin 60 mg/m^2 given via rapidly flowing IV infusion Note: FLT3-positive participants may receive cytarabine 200 mg/m^2/day	• Dociparstat 4 mg/kg or placebo IV bolus on Day 1, administered 30 minutes after completion of the first dose of idarubicin or daunorubicin, **followed by** • Dociparstat 0.25 mg/kg/hr or placebo by continuous IV infusion for 24 hours daily for 5 days (starting on Day 1 and ending on Day 6 [120 hours])
Consolidation cycles (up to 4 cycles, as applicable)	Only participants with a documented response (CR or CRi) are eligible for consolidation. • Cytarabine via IV infusion over 3 hours, administered twice daily (at 12-hour intervals) on Day 1, Day 3, and Day 5 o Age 18-59 years: 3 g/m^2/dose o Age ≥60 years: 1.5 g/m^2/dose	• Dociparstat 4 mg/kg or placebo IV bolus on Day 1, administered 30 minutes after completion of the first dose of cytarabine, **followed by** • Dociparstat 0.25 mg/kg/hr or placebo by continuous IV infusion for 24 hours daily for 5 days (starting on Day 1 and ending on Day 6 [120 hours])

Note: Participants with a FLT3 mutation may also receive treatment with midostaurin at the investigator's discretion and dependent on local availability.

6.2. Preparation, Handling, Storage, and Accountability

6.2.1. Dose Preparation

Dosing will be calculated on the basis of each participant's weight for study intervention and body surface area for chemotherapy (cytarabine, daunorubicin, and idarubicin). It is recommended that the dosing calculations and preparation of each dose of study intervention be confirmed by a second unblinded pharmacist.

Preparation of randomized study intervention (i.e., dociparstat or placebo) will be performed by an unblinded pharmacist within the investigational pharmacy. The pharmacist will prepare study intervention to the appropriate calculated dose. Normal saline will be used to dilute the IV bolus dose and continuous maintenance infusion of dociparstat. The dociparstat IV bolus dose will be diluted to a total infusion volume of 30 mL. The 24-hour continuous infusion will have the appropriate volume of dociparstat added to approximately 250 mL or 500 mL of 0.9% normal saline.

The placebo IV bolus dose will be a total infusion volume of 30 mL of 0.9% normal saline only. Placebo for the continuous infusion will be 250 mL or 500 mL of 0.9% normal saline only.

Only participants randomized in the study may receive study intervention and only authorized site staff may prepare, supply, or administer study intervention.

All study intervention syringes and bags need to be blinded (masked) after final preparation and prior to leaving the pharmacy. Sites will follow their own labeling procedures to identify prepared study intervention (i.e., dociparstat or placebo) for each participant in a blinded manner.

Refer to the product labels for information on preparation and administration of cytarabine, daunorubicin, and idarubicin.

6.2.2. Handling, Storage, and Accountability

A sufficient quantity of vials of dociparstat solution for injection will be supplied to the investigator (or qualified designee) at each study center. Once received at the study center, kits of dociparstat should be stored in accordance with the labeled storage conditions, in a securely locked area, with access limited to the unblinded pharmacist and authorized site staff. [**Note**: The labeled storage conditions are dependent on the manufactured drug product batch/lot.]

The investigator or qualified designee (e.g., unblinded pharmacist) must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and must report and resolve any discrepancies before use of the study intervention.

The investigator or qualified designee (e.g., unblinded pharmacist) is responsible for ensuring adequate accountability of all used and unused study intervention. This includes acknowledgment of receipt of the shipment(s) of study intervention (date, quantity, condition, and vial numbers), participant dispensing records (date, participant number, and vial number), and returned or destroyed vials. All study intervention records must be maintained at the site and copies must be submitted to Chimerix at the end of the study. The unblinded investigator designee should promptly inform the unblinded study monitor of any discrepancies in accountability of study intervention.

After verification of the study intervention records by the unblinded study monitor, all remaining study intervention supplies should be destroyed according to directions provided by Chimerix (or its designee) and/or any applicable site-specific standard operating procedures. If necessary, unused study intervention supplies may be returned to the appropriate depot with prior approval from Chimerix (or its designee). If study intervention is destroyed on site, the investigator must maintain accurate records for all study intervention destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and person who disposed of the drug.

Refer to the product labels for information on handling and storage of normal saline, cytarabine, daunorubicin, idarubicin, and ancillary supplies (e.g., IV bags and tubing).

6.3. Dose Modification

All participants randomized into the study will be treated with an initial induction cycle of blinded study intervention plus standard 7+3 chemotherapy starting on Day 1. The total number of treatment cycles administered to each participant is determined by the investigator through evaluations of treatment response, potential toxicity or tolerability issues, and suitability for alternate treatments (e.g., HCT).

There are no modifications in the mg/kg dosing of blinded study intervention. Criteria for interruption and discontinuation of study intervention are provided in Section 7.

6.4. Measures to Minimize Bias: Randomization and Blinding

A randomized, double-blind, placebo-controlled study design was selected as the most robust design to minimize potential bias.

Participants who meet all applicable eligibility criteria will be centrally randomized to one of two study intervention groups (dociparstat or placebo) in a 1:1 ratio using an automated IRT system and a computer-generated randomization code provided by the sponsor or designee. Randomization will be stratified based upon FLT3 status (FLT3+ vs FLT3-), genetic risk (intermediate vs adverse), and age (<65 years vs ≥65 years).

Once a randomization number has been assigned, it will not be re-assigned to any other participant in the study. The IRT system will also be used to track study intervention dispensing.

Investigators, participants, and sponsor personnel (to the extent practicable) will be blinded to each participant's assigned study intervention throughout the course of the study. In order to maintain this blind, an otherwise uninvolved third party (an unblinded study pharmacist) will be responsible for the preparation and dispensation of blinded study interventions (i.e., dociparstat and placebo) and will ensure that there are no differences in appearance or time taken to dispense study intervention following randomization.

In the event of a regulatory inspection or quality assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization and dispensing have been done accurately. Additional roles and responsibilities that require unblinding of specified sponsor (and/or designated contract research organization) personnel not directly involved in the conduct of the study include supply chain, regulatory reporting of expedited safety reports, and data monitoring committee (DMC) reviews.

Normal saline (sodium chloride 0.9%) will be used as the study intervention placebo for both the loading doses and the continuous infusions. Placebo-controlled studies are the gold standard for clinical trials, as they reduce bias in care and conduct during the study. Though the efficacy endpoints are objective, safety assessments are less biased when treatment allocation is masked. Most importantly, downstream decisions regarding postinduction therapy are best made without knowledge of initial treatment assignment to reduce possible bias in this study.

Modest effects of dociparstat on aPTT have been observed in previous studies. Although the Phase 2b mean aPTT values during the continuous infusion were nominally higher for dociparstat 0.25 mg/kg than control, the individual participant values were variable and had considerable overlap between groups; therefore, individual aPTT measurements are not expected to unblind the participant's treatment assignment. In this Phase 3 study, potential unblinding will be mitigated by obtaining initial aPTT measurements no sooner than 8 hours after the IV bolus (after the time of peak effect) and by instructions to obtain blood for aPTT measurements from a location that is separate from the dociparstat infusion. Specifically, blood should be obtained via separate venipuncture and/or a catheter separate from the one used to administer study intervention. If the specimen is drawn from a heparinized line, first draw 5 mL of blood from the line for discard before drawing the aPTT sample.

Emergency unblinding: The IRT system will be used for blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

6.5. Study Intervention Compliance

Participants will receive study intervention and standard of care chemotherapy directly from the investigator or qualified designee, under medical supervision. The date and start/stop times of each dose of study intervention and standard of care chemotherapy administered will be recorded in the source documents and in the eCRF.

Study participant identification and dose of study intervention will be confirmed at the time of dosing by a member of the site staff other than the person administering the study intervention.

6.6. Concomitant Therapy

Information about the participant's concomitant medications/therapies will be collected in the eCRF as specified below.

Collection time periods:

- Prior medications: All medications taken from 30 days prior to the time of signing the informed consent form (ICF) through the time of randomization.

- Concomitant medications: All medications and transfusions from the time of first dose of study intervention on Day 1 through 42 days after the start of the last treatment cycle (induction, reinduction, or consolidation, whichever is later).
- Follow-up: Only AML therapies (i.e., for the treatment of AML and/or prevention of relapse) from 43 days after start of last treatment cycle through the time of last study follow-up.

Information to collect:

- Names (nonproprietary names are preferred) for all prescription medications and growth factors, and details of transfusions (do not need to collect use of vitamins, supplements, or IV fluids).
- Reason for use (indication).
- Start and end dates of administration.
- Dosage information, including dose, units, route, and frequency.

Contact the medical monitor (or designee) if there are any questions regarding concomitant or prior therapy.

6.6.1. Prohibited Therapies

Refer to the exclusion criteria (see Section 5.2) for medications prohibited prior to randomization (and the associated time period) in the study.

The following medications are prohibited throughout the duration of the treatment period (i.e., during protocol-specified induction and consolidation treatment cycles, unless otherwise specified):

- AML treatments not specified in the protocol, including (but not limited to) the following:
  - Vyxeos (daunorubicin and cytarabine liposome for injection)
  - Myelotarg (gemtuzumab ozogamicin)
  - Venetoclax
  - Decitabine or azacitidine
  - Isocitrate dehydrogenase (IDH) inhibitors (e.g., Tibsovo [ivosidenib], Idhifa [enasidenib])
  - Mitoxantrone
- Hematopoietic growth factors during induction and reinduction cycles.
- Anticoagulants (e.g., unfractionated heparin, low molecular weight heparin, warfarin, factor Xa inhibitors) [If a participant requires short-term anticoagulant therapy, see Section 7.1]. Heparin flush of indwelling catheters is permitted. Discuss use of other agents for catheter occlusion with the medical monitor.
- Investigational agents.

6.6.2. Permitted Therapies

The following medications are permitted during the study:

- Midostaurin: Participants who are known to have a FLT3 mutation may, at the investigator's discretion and dependent on local availability, receive midostaurin in accordance with the product label.
- Infection prophylaxis and treatment, and transfusion support – according to institutional standard of care.
- Granulocyte colony-stimulating factor (G-CSF) following consolidation therapy.

  If used, recommended treatment is a single dose (per package labeling) of peg-filgrastim/liposomal G-CSF (Neulasta or biosimilar) administered subcutaneously 24 to 48 hours after the last dose of cytarabine consolidation in participants who have achieved an MRD_{neg} CR or CRi after induction/reinduction. Alternatively, other G-CSF agents may be used after consolidation therapy per institutional standard of care and package labeling.

6.7. Intervention after the End of the Study

Dociparstat is intended for use as up-front treatment in combination with standard induction and consolidation chemotherapy in participants with newly-diagnosed AML. Since dociparstat is not intended for continued maintenance treatment, the study intervention will not be provided beyond the protocol-specified treatment period.

After the end of the treatment period, the participants' ongoing medical care and treatment in the event of a recurrence will be the responsibility of the participants' physician(s).

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Interruption of Study Intervention

Infusion of study intervention (i.e., dociparstat or placebo) will be interrupted in the following situations:

aPTT: Participants with aPTT >45 seconds will have repeat testing performed as soon as practicable. If aPTT is confirmed >45 seconds, interrupt the study intervention infusion. To minimize time that the participant is off therapy, perform repeat testing for aPTT approximately 2 to 6 hours after interruption (as practicable). Infusion may be resumed once aPTT is <35 seconds. **Note**: samples are not to be obtained from the same line as study intervention infusion (e.g., collect via peripheral venipuncture).

Grade 3 or higher hemorrhagic AEs: Study intervention infusion will be interrupted for Grade 3 or higher hemorrhagic AEs in the setting of aPTT >40 seconds, or Grade 3 or higher hemorrhagic AEs that are deemed to be related to study intervention, regardless of aPTT. Study intervention infusion may be resumed once the participant is determined to be stable and the aPTT is <35 seconds.
Note: Grade 3 or higher hemorrhagic AEs are also considered AEs of special interest.

Renal function: If the calculated creatinine clearance drops below 30 mL/min or eGFR drops below 30 mL/min/1.73 m^2 prior to or during dosing with study intervention, the infusion will be held until the creatinine clearance or eGFR rises to ≥30.

Electrocardiogram (ECG)/QTc: Study intervention infusion will be interrupted if a participant meets any of the following criteria (based on the average of triplicate ECG readings; see Section 8.3.3 for details about QTc correction formulas):

- Without underlying bundle branch block:
  - Interrupt for QTc >500 msec OR uncorrected QT >600 msec,
- With underlying bundle branch block:
  - If baseline QTc <450 msec, then interrupt for QTc >500 msec
  - If baseline QTc 450 to 480 msec, then interrupt for QTc >530 msec

In the event of prolonged QTc, the participant should also be assessed for other medications that may impact QT interval (see Appendix 6: Drugs Known to Prolong the QT Interval), with any necessary changes made to concomitant medications. Infusion of study intervention may be resumed once QTc is <480 msec. Following resumption of infusion, ECGs are to be checked daily until the participant has had 3 consecutive (daily) tracings with QTc <480 msec, after which follow-up ECGs will be as per institutional standard of care. Report any new, clinically-relevant finding as an AE.

Bilirubin: If total bilirubin is >2 mg/dL, refer to the daunorubicin/idarubicin product label for dosage adjustments. No adjustment to the study intervention dosing is recommended.

Anticoagulant therapy: If a participant requires short-term anticoagulant therapy, interrupt the administration of study intervention. Infusions may be resumed if anticoagulant therapy is discontinued and aPTT is <35 seconds.

Note: If study intervention is interrupted and not restarted during the same treatment cycle, the participant may receive study intervention (bolus and infusion) during the next treatment cycle (assuming the participant no longer meets any of the interruption criteria).

Reasons for dose interruption will be entered into the eCRF. The total daily volume of IV solution infused (obtained directly from the IV pump data) will be recorded in the comment section of the eCRF for each participant who requires dose interruption.

7.2. Discontinuation of Study Intervention

In some instances, it may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention may include the following:

- Participant did not achieve CR/CRi at the end of the reinduction treatment cycle.
- Criteria for restarting study intervention after interruption were not met.
- Treatment-related AE of unacceptable severity.
- Participant requests to discontinue study intervention.
- Investigator determines discontinuation is in the best interests of the participant for safety, behavioral, compliance, administrative, or other reasons.

Participants who discontinue study intervention early will complete the early discontinuation assessments (refer to the Schedule of Activities/Assessments; Section 1.2) and will continue to be followed-up for outcomes in the long-term follow-up period of the study until death or for 5 years after randomization.

7.3. Participant Withdrawal from the Study

- It is expected that all participants randomized in the study, regardless of completion or discontinuation of study intervention, will remain in the study for long-term follow-up.
- Before withdrawing a participant from the study, clarify and document the specific expectations of the participant's request for withdrawal. The following withdrawal scenarios may apply:
    - Discontinuation of study intervention, but completes remaining study assessments, and agrees to collection of relevant follow-up information (i.e., remains in the study; this is the default scenario).
    - Discontinuation of study intervention and/or refuses further study-specific assessments, but agrees to collection of relevant follow-up information (i.e., remains in the study).
    - Completion or discontinuation of study intervention and/or refuses further assessments, AND withdraws consent for any further study communication or

follow-up from the study center (i.e., withdraws from the study); the investigator must document this in the site study records.

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- At the time of withdrawing from the study, if possible, an early withdrawal visit will be conducted. See the Schedule of Activities/Assessments (Section 1.2) for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested; the investigator must document this in the site study records.

Discontinuation of specific sites or of the study as a whole are discussed in Appendix 1.

7.4. Lost to Follow-up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and the study center is unable to contact the participant.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study. The sponsor may retain and continue to use any data collected.
- The site should also make every effort to verify the participant's vital status with the participant's regular/non-study physician(s).

8. STUDY ASSESSMENTS AND PROCEDURES

Planned time points for all study assessments and procedures are provided in the Schedule of Activities/Assessments (see Table 1 for induction cycles and Table 2 for consolidation cycles). Adherence to the study design requirements, including all specified assessments, is essential and required for study conduct. Protocol waivers or exemptions are not allowed.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with sample quality. Record results of any unscheduled assessments or visits related to study participation in the eCRF.

8.1. Screening

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure.

Procedures conducted as part of the participant's routine clinical management (e.g., blood counts) and obtained before signing of the ICF may be utilized for screening or baseline purposes, provided the procedures meet protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities/Assessments (Table 1). Applicable results must be entered into the participant's eCRF.

The following examinations and procedures will be conducted as part of the screening process:

- Informed consent. Written documentation of completion of the informed consent process with the potential participant (and legally authorized representative if applicable).
- Demographics, medical history (including family medical history), medication history, ECOG status (see Appendix 5), physical examination, vital signs, height, and weight.
- ECG (see Section 8.3.3).
- Echocardiogram or multigated acquisition (MUGA) scan to identify pre-existing cardiac dysfunction that may exclude a participant from enrollment or contraindicate use of standard 7+3 chemotherapy. Repeat testing before subsequent cycles of chemotherapy will be per institutional standard of care.
- Clinical chemistry, hematology, fibrinogen, D-dimer, and coagulation (aPTT, prothrombin time/international normalized ration [PT/INR]) tests (see Section 8.3.4).
- Analysis of bone marrow aspirate/biopsy and peripheral blood screening samples (see Section 8.2.1) for confirmation of diagnosis, identification of specific translocations and inversions, and determination of genetic risk categorization and study eligibility.
- Review of all eligibility criteria to determine if participant qualifies for randomization. This includes review of results of all screening assessments and a final review for any changes in medical history, concomitant medications, or ECOG status at baseline before randomization.

8.2. Efficacy Assessments

The anti-leukemic activity of dociparstat in combination with 7+3 chemotherapy will be assessed by routine laboratory tests and examination of bone marrow aspirates/biopsies. Response criteria and outcome measures are based on definitions from ELN (Döhner 2017; also see Appendix 7).

8.2.1. Bone Marrow Aspirate/Biopsy and Peripheral Blood Assessments

Bone marrow aspirate/biopsy and peripheral blood samples will be collected for the assessments specified in Table 6. Tests such as cytogenetic analyses are commonly performed locally for diagnosis of AML; central molecular genetic testing and using fluorescence in situ hybridization (FISH) is performed to facilitate rapid turnaround of tests for purposes of determining eligibility and stratification. If there is a discrepancy between results from central and local laboratories, results from the central laboratory will be used for determination of eligibility and stratification.

MRD testing of screening bone marrow samples is critical to identify leukemia associated phenotypes that are to be followed at each recovery assessment. Due to the need for high quality samples that are not hemodiluted, the ELN strongly recommends that the first bone marrow aspirate draw be used for MRD assessment.

Table 6: Bone Marrow and Peripheral Blood Efficacy Assessments

Assessment	**Purpose**	**Laboratory** • **Sample Type**	**Timing**
Multiparameter (multicolor) flow cytometry (MFC) (also see Table 9)	MRD analysis	Central laboratory • Bone marrow aspirate (***first draw***)	• Screening • Time of hematologic recovery for each treatment cycle
Biobanking (also see Table 9)	Storage and future analyses	Central laboratory • Bone marrow aspirate • Whole blood	• Screening • Time of hematologic recovery for each treatment cycle
Immunological phenotyping	Expression of cell-surface and cytoplasmic markers	Central laboratory [a] • Whole blood	• Screening
Fluorescence in situ hybridization (FISH)	Identification of rearrangements including RUNX1-RUNX1T1, CBFB-MYH11, KMT2A (MLL), and MECOM (EVI1)	Central laboratory [a] • Whole blood	• Screening
Molecular genetic testing	Including mutations in FLT3, NPM1, CEBPA, RUNX1, TP53, and ASXL1	Central laboratory [a] • Whole blood	• Screening

Assessment	Purpose	Laboratory • Sample Type	Timing
Morphology (cytology)	Identification of marrow cellularity and blast percentage	Local – Enter results in eCRF • Bone marrow aspirate	• Screening • After each treatment cycle
Cytogenetic profile (cell culture and banding analyses)	Identification of specific translocations and inversions	Local – Enter results in eCRF • Bone marrow aspirate	• Screening

[a] In the event the central laboratory is not able to analyze a sample or results are delayed, local laboratory results (if available) *may* be utilized for screening/eligibility.

Study center staff must enter results of all local/institutional bone marrow analyses into the eCRF. Copies of all local pathology reports are to be retained with the participant's study records and to be available for monitoring.

Instructions for collection, handling, and shipment of samples is included in the laboratory manual.

8.2.2. Response Criteria and Outcome Measures

Response criteria and outcome measures (Table 7) are based on definitions from ELN (Döhner 2017).

Table 7: Response Criteria and Outcomes Measures

Response / Outcome		Definition
Response	Complete remission with complete hematologic recovery (CR)	Defined for all study participants at the end of induction therapy. Bone marrow blasts <5%, absence of circulating blasts and blasts with Auer rods, absence of extramedullary disease, ANC >1.0 x 10^9/L (1000/µL), and platelet count >100 x 10^9/L (100,000/µL). Recovery of ANC and platelet counts within 7 days before or 7 days after bone marrow biopsy showing blasts <5% may be used to assess best response.
	CR with incomplete hematologic recovery (CRi)	Defined for all study participants at the end of induction therapy. All CR criteria (bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease), except for residual neutropenia (≤1.0 x 10^9/L [1000/µL]) or residual thrombocytopenia (≤100 x 10^9/L [100,000/µL]). [Note: Participants with both residual neutropenia and residual thrombocytopenia are not considered to have achieved CRi.]
	CR with partial hematologic recovery (CRh)	Defined for all study participants at the end of induction therapy. CR criteria (bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease), with partial recovery of peripheral blood counts (ANC >0.5 x 10^9/L [500/µL] and partial recovery of platelets >50 x 10^9/L [50,000/µL], but the count recovery criteria for CR are not met).

Response / Outcome		Definition
	Measurable residual disease negative (MRD_{neg})	Defined for all study participants at the end of induction and consolidation therapy. Negative (undetectable) MRD in recovery (~Day 22-42) bone marrow, as measured by MFC (0.1% detection limit).
Failure	Treatment failure (induction failure)	Failure to achieve CR (or CR/CRi) within 42 days of the start of induction therapy (or start of reinduction therapy when applicable).
Relapse	Relapse (hematologic)	Defined through 5 years after randomization only for participants achieving CR (or CR/CRi) during induction/reinduction. After achievement of CR/CRi, bone marrow blasts ≥5%, reappearance of blasts in the blood, or development of extramedullary disease.
	Cumulative incidence of relapse	Defined through 5 years after randomization only for participants achieving CR (or CR/CRi) during induction/reinduction. Measured from the date of randomization to the date of relapse. Participants not known to have relapsed will be censored on the date they were last known to be alive. Participants who die without relapse will be counted as competing-risk events.
Outcome Measure	Overall survival (OS) ***Primary Endpoint**	Defined for all study participants through 5 years after randomization. Measured from the date of randomization to date of death from any cause. Participants not known to have died at last follow-up contact will be censored on the date they were last known to be alive.
	Event-free survival (EFS) following CR ***Key Secondary Endpoint**	Defined for all study participants through 5 years after randomization. Measured from the date of randomization to treatment failure, relapse, or death from any cause, whichever occurs first. For this endpoint, treatment failure is defined as failure to achieve CR within 42 days of the start of induction/reinduction. Participants not known to have relapsed or died will be censored on the date they were last known to be alive.
	EFS following CRi	Defined for all study participants through 5 years after randomization. Measured from the date of randomization to treatment failure, relapse, or death from any cause, whichever occurs first. For this endpoint, treatment failure is defined as failure to achieve CRi within 42 days of the start of induction/reinduction. Participants not known to have relapsed or died will be censored on the date they were last known to be alive.
	Relapse-free survival (RFS)	Defined through 5 years after randomization only for participants achieving CR (or CR/CRi) during induction/reinduction. Measured from the date of randomization to date of relapse or death from any cause. Participants not known to have relapsed or died at last follow-up contact will be censored on the date they were last known to be alive.
	Time to recovery of neutrophil count	Defined for all study participants. Measured as time from date of randomization until the first day the ANC is >500/μL and is >1000/μL following induction or reinduction (if indicated).

Response / Outcome		Definition
	Time to transfusion-independent platelet recovery	Defined for all study participants. Measured as time from date of randomization until the first day the platelet count recovers to >20,000/μL, >50,000/μL, and >100,000/μL, without a platelet transfusion in the preceding 5 days following induction or reinduction (if indicated).

8.2.3. Long-Term Follow-up

After completion or discontinuation of study intervention, participants will be followed-up until death or for 5 years after randomization. Contact with the participant (or caregiver or treating physician, as applicable) will be made every 3 months for the first 24 months, then every 6 months for the remaining follow-up period.

At (suspected) relapse, a full bone marrow examination should be performed, including morphology, cytogenetics, and biobanking; also collect peripheral blood for immunological phenotyping, molecular diagnostics, and biobanking. Participants will be asked to notify the study center in the event of relapse, even if a different physician/institution will be handling their future care.

The following information will be collected as applicable: disease status (relapse date) (may include results of tests used for diagnosis of recurrence), death date, cause of death, and related source documentation. In addition, all AML therapies (i.e., for the treatment of AML and/or prevention of relapse) will be collected from 43 days after start of the last treatment cycle through the time of last study follow-up; this includes HCT and/or CAR T cell date(s) and details, other chemotherapy agent start/stop dates (and reasons for the treatment choice), and maintenance therapy start/stop dates.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Activities/Assessments (see Table 1 and Table 2).

The investigator will discuss any immediate safety concerns with the sponsor (or designee) upon occurrence or awareness to determine if the participant should continue or discontinue receiving study intervention.

Safety data will be monitored by an independent DMC on a routine basis (see Section 9.6).

8.3.1. Physical Examinations

Measure height at screening; measure weight (without shoes) at screening and at the start of consolidation therapy.

Determine ECOG status (see Appendix 5 for details) at screening and confirm status at baseline before the first dose of study intervention.

Complete a physical examination at screening as part of the review for eligibility for the study. Investigators should pay special attention to clinical signs related to AML and any other previous or ongoing serious illnesses. Record any clinically-relevant findings in the eCRF as medical history.

During the treatment period of the study (i.e., after the first dose of study intervention), record any clinically-relevant change(s) in physical examination (obtained during routine standard of care) findings in the eCRF as an AE(s).

8.3.2. Vital Signs

Assess all vital signs (temperature, pulse rate, respiratory rate, and blood pressure) at screening as part of the review for study eligibility. Record any clinically-relevant findings as medical history in the eCRF.

During the treatment period of the study, record any clinically-relevant change(s) in vital sign measurements (obtained during routine standard of care) in the eCRF as an AE(s).

8.3.3. Electrocardiograms

ECGs will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

As specified in the Schedule of Activities, 12-lead ECGs will be obtained at the following time points:

- Screening
- Baseline/Day 1 predose
- Day 1 at the end of the study intervention (i.e., dociparstat or placebo) bolus dose
- Day 8 at the end of the study intervention (i.e., dociparstat or placebo) infusion for the initial induction cycle
- Additional readings may be necessary to monitor AEs and/or changes in ECG measurements (e.g., as described in Section 7)

At screening, 3 individual ECG tracings should be obtained as closely as possible in succession, but ideally no more than 2 minutes apart, with the full set of triplicates completed in less than 4 minutes. At subsequent time points, a single ECG tracing will be obtained, with a repeat tracing to confirm QTc intervals >480 msec.

Refer to Section 5.2 for QTc-related criteria for participant exclusion and Section 7 for QTc-related criteria for interruption and discontinuation of study intervention.

At screening, as part of the review for eligibility for the study, and at baseline prior to the first dose of study intervention, record any clinically-relevant ECG findings as medical history in the eCRF. During the treatment period of the study, record any clinically-relevant change(s) in ECGs (obtained at protocol-specified time points or during routine standard of care) in the eCRF as an AE(s).

It is recommended that QTc be calculated using Fridericia's formula (QTcF) for all participants. If a study center does not have access to an ECG machine capable of calculating QTcF, then correction using an alternate formula may be used. All recordings for a single participant must use the same correction formula; therefore, if one formula is used at screening to determine eligibility for enrollment, that same formula must also be used during treatment to determine if criteria have been met for interruption or discontinuation of study intervention.

8.3.4. Clinical Safety Laboratory Assessments

All required laboratory assessments must be conducted in accordance with this protocol and the laboratory manual. The timing and frequency of laboratory assessments are specified in the Schedule of Activities (Table 1 and Table 2).

- The laboratory tests (clinical chemistry, hematology, and coagulation) listed in Table 8) will be performed by the study centers' usual local laboratory.
- All laboratory reports will be filed with the source documents.
- Site personnel must enter results into the eCRF for the specified laboratory parameters (with units and relevant reference ranges) at each specified time point.
- The investigator must document their review of each laboratory report. Clinically-relevant abnormal laboratory findings at screening and before the first dose of study intervention will be recorded as medical history.
- Clinically-significant abnormal changes occurring during the treatment period of the study or within 42 days after the start of the last cycle of study intervention will be recorded in the eCRF as an AE(s). Clinically-significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
  - These laboratory tests will be repeated (and recorded in the eCRF) until the values return to normal or baseline or are no longer considered clinically significant by the investigator.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified.
  - The investigator may consult with the medical monitor for any questions.

Laboratory tests may be performed at additional times during the study as part of standard care, as determined necessary by the investigator, or as required by local regulations. Any laboratory test(s) performed in response to an AE and any laboratory results that are used for decisions regarding participants' treatment response, study interventions, and/or AML treatments must be recorded in the participants' eCRF (as an unscheduled visit if not at a protocol-specified time point).

Refer to Section 5.2 for laboratory-related criteria for participant exclusion and Section 7 for laboratory-related criteria for interruption and discontinuation of study intervention.

Table 8: Laboratory Assessments

Laboratory Assessments	Parameters for Routine Monitoring	Additional Screening Parameters
Hematology	• Platelet Count • Hemoglobin • Absolute neutrophil count • White blood cell count with differential (unless count is too low) • Peripheral blast count • Blasts with Auer rods	*Screening only:* Hematocrit, red blood cell (RBC) count
Clinical Chemistry	• Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Total and direct bilirubin • Alkaline phosphatase • Blood urea nitrogen • Creatinine • Lactate dehydrogenase • Calcium • Magnesium • Potassium • Sodium	*Screening only:* Chloride, phosphate, albumin, total protein, glucose, uric acid, gamma-glutamyl transferase
Coagulation	• Activated partial thromboplastin time (aPTT) • Prothrombin time and international normalized ratio (PT/INR)	*Screening only:* Fibrinogen, D-dimer

8.4. Adverse Events and Serious Adverse Events

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for follow-up.

AEs will be categorized by system organ class and preferred term using the Medical Dictionary for Regulatory Activities dictionary and AE severity will be graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE).

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

Any SAE that is considered related to study procedures will be collected from the time of consent until the first dose of study intervention. Any other medical occurrences that begin during this time period will be recorded on the medical history/current medical conditions section of the eCRF (not as an AE/SAE).

All AEs will be collected from the time of first dose through 42 days after the start of the last treatment cycle with study intervention (i.e., dociparstat or placebo administered during initial induction, reinduction, or consolidation therapy as specified in this protocol).

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 2: Adverse Events. The investigator will submit any updated SAE data to the sponsor within 24 hours of the data being available.

Investigators are not obligated to actively seek new onset AEs or SAEs after the protocol-defined reporting period; however, if the investigator learns of any SAE and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After an initial AE or SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. It is important for all SAEs, AEs of special interest (as defined in Section 8.4.7), AEs considered related to study intervention, and AEs that resulted in discontinuation of study intervention to be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4).

8.4.4. Regulatory Reporting Requirements for SAEs

Prompt notification of an SAE by the investigator to the sponsor is essential so that legal and regulatory obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and be forwarded to investigators as necessary. An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5. Death Events

If a participant dies during participation in the study (at any time from the time of consent through long-term follow-up), the investigator will provide the date of death and a determination of cause of death (including any supporting information, such as death certificate, pathology or autopsy information, as applicable).

All deaths from events with onset through 42 days after the start of the last treatment cycle with study intervention are to be reported as SAEs. Thereafter, the investigator will provide the requested information in the eCRF along with requested supporting information.

8.4.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

The following disease-related events may be serious and life-threatening and are common in participants with AML:

- AML progression
- Thrombocytopenia
- Neutropenia

Because thrombocytopenia and neutropenia are typically associated with the disease under study, when the event(s) occurs with active leukemia, it is not to be reported by the investigator as an AE/SAE, unless the event meets one or more of the following conditions. If any of these conditions apply, then the event must be recorded and reported as an AE/SAE:

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.
- The investigator considers that there is a reasonable possibility that the event is related to study intervention.

8.4.7. Adverse Events of Special Interest

Adverse events of special interest, as listed below, must be recorded and reported to the sponsor (or designee) within 24 hours.

- Prolonged neutropenia:
  Defined as a case of Grade 4 neutropenia that, in the absence of active leukemia, lasts past Day 42 of a chemotherapy cycle.
- Hemorrhagic AEs that are Grade 3 or higher in severity (per CTCAE criteria):
  Additional information about hemorrhagic AEs will be collected to more fully describe the participant's status and assess potential causes and contributing factors; this includes, at a minimum, aPTT values, platelet values, possible contributory medications (e.g., heparin or other anticoagulants) in the preceding 7 days, and treatment(s) administered.

8.5. Treatment of Overdose

For this study, any dose of study intervention (i.e., dociparstat or placebo) greater than 8 mg/kg as a bolus dose, greater than 0.5 mg/kg/hr infusion, or greater than 20 mg/kg within a 24-hour time period will be considered an overdose.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately.
- If the continuous infusion is ongoing, adjust the rate to administer the correct dose.
- Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 48 hours after the overdose.
- Document the quantity of the excess dose and the duration of the overdose in the eCRF.

Interrupt the study intervention infusion if clinically-significant bleeding (e.g., Grade 3 or higher hemorrhagic AE) or aPTT >45 seconds occurs after administration of an overdose of dociparstat (see Section 7.1). Other decisions regarding dose interruptions will be made by the investigator in consultation with the medical monitor based on clinical evaluation of the participant.

At the discretion of the investigator in consultation with the medical monitor, protamine may be used to neutralize the anticoagulation effects of dociparstat overdose. Protamine doses should be based on activated clotting time or aPTT plasma values and not based on the milligram dosage of dociparstat administered.

In the event of an overdose of cytarabine, idarubicin, or daunorubicin, refer to the approved product label(s) for guidance.

8.6. Pharmacokinetics

During the initial induction cycle, plasma samples (~2 mL) will be collected for analysis of dociparstat concentrations to derive pharmacokinetic parameters, as data permit.

Plasma samples will be collected at the following time points:

- Day 1: predose; at the end of the IV bolus; and at 1 hour and 12 hours after the end of the IV bolus.
- Day 4: a single sample will be collected during the infusion (ideally in the morning).
- Day 8: within ~5 minutes after the end of the infusion, and at 0.5, 1, 2, and 4 hours after the end of the infusion.

Blood samples will ideally be collected within ±10 minutes of the specified time points. The date and **actual time** (24-hour clock time) **must be recorded** for each blood sample. The timing of sampling may be altered during the study based on newly available data and up to 3 samples may be collected at additional time points (if warranted and agreed upon between the investigator and the sponsor) to ensure appropriate monitoring.

Note: Do not draw blood from the same line that is used for study intervention administration. Drawing blood from a heparinized line may falsely alter the PK results obtained; therefore, if

using an indwelling catheter, draw approximately 5 mL of blood for discard before drawing the PK sample. Additional information regarding sample collection and handling is provided in the laboratory manual.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Pharmacokinetic parameters to be evaluated include area under the concentration-time curve (AUC), maximum observed concentration (Cmax), time to maximum observed concentration (Tmax), terminal elimination half-life ($t_{½}$), and clearance. Plasma samples collected for analyses of dociparstat concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

PK samples will be collected at study centers with appropriate capabilities (e.g., centrifuge, staff experience and availability).

8.7. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.8. Genetics

Genetic variation may impact a participant's response to study intervention and susceptibility to, severity of, and progression of disease. An optional saliva specimen or buccal swab will be obtained for germ-cell line analysis. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated.

Cytogenetic Analyses

Cytogenetic testing of bone marrow samples is a required screening test to appropriately type and characterize AML and to determine eligibility for study enrollment based on intermediate or adverse/unfavorable genetic risk.

Biobanking

Where local regulations and IRB/IEC allow, a 10-mL bone marrow sample and a 10-mL whole blood sample will be collected at designated time points for biobanking from participants who have consented to participate in this component of the study.

- Whole blood and bone marrow will be processed at the central lab to isolate cells for cryopreservation to maintain viability.
- Retrospective analysis on cryopreserved cells and/or extracted nucleic acids from biobanked samples will be conducted for research related to biomarkers of response/resistance to study drugs and mechanism of action for dociparstat. This could allow for developing tests/assays to predict response and resistance to the study drugs, including dociparstat.

- The results of genetic analyses may be reported in the clinical study report or in a separate study summary report.
- The sponsor will store the samples (cells, DNA or RNA) in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on dociparstat continues, but no longer than 15 years or other period as per local requirements.

Participation in biobanking is strongly encouraged, but optional. Participants who do not wish to participate in biobanking may still participate in the study.

Details on processes for collection, shipment, and destruction of these samples is included in the laboratory manual.

8.9. Biomarkers

- For all participants, bone marrow aspirate/biopsy samples will be collected and tested for MRD via MFC at screening and after hematologic recovery for each cycle of induction and consolidation chemotherapy (as specified in the Schedule of Activities) to evaluate the association with dociparstat treatment and the observed OS and EFS.
- Blood samples will be collected during induction and consolidation therapy to measure plasma levels of HMGB1, which is expressed in tumor tissues and higher levels have been correlated with worse clinical prognosis. The association of dociparstat with lower HMGB1 levels will be evaluated. See Section 1.2 for collection timepoints. For participants who receive multiple consolidation cycles, only samples from the last consolidation cycle will be analyzed. Blood samples collected for HMGB1 may be reserved for batch analysis. Refer to the laboratory manual for instructions on collection of a separate sample, versus using blood from the biobanked sample for analysis.
- Biobanked blood and bone marrow may be used to conduct retrospective analyses of biomarkers including, but not limited to, CXCR4, CXCR7, CXCL12, and LSC markers to evaluate their association with observed clinical responses and gain insight into the mechanism of action of dociparstat in AML treatment. Genetic markers known to be related to AML response and or resistance (e.g., clonal selection for TP53 and FLT3 variants) may be examined and additional analyses may be conducted to advance understanding of potential predictors for response (e.g., gene signatures associated with LSCs).

Details on processes for collection, shipment, and destruction of these samples is included in the laboratory manual.

Table 9: Sample Collection Time Points for MRD Analyses and for Biobanking

Sample Time	Analysis	Sample Material
Screening	MRD + Biobanking	10 mL Bone marrow 10 mL Whole blood
Recovery after initial induction (Day ~28-42)	MRD + Biobanking	10 mL Bone marrow 10 mL Whole blood
Recovery after reinduction (Day ~28-42)	MRD + Biobanking	10 mL Bone marrow 10 mL Whole blood
After each consolidation cycle	MRD + Biobanking	10 mL Bone marrow 10 mL Whole blood
Relapse	MRD + Biobanking	10 mL Bone marrow 10 mL Whole blood

8.10. Medical Resource Utilization

Dates of hospitalization and discharge, and number of days spent in intensive care settings will be assessed. Number of blood product units (e.g., red blood cell transfusions, platelet transfusions) administered and number of growth factor administrations will also be collected.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The null hypothesis is that the effect of dociparstat plus standard chemotherapy on OS and EFS equals the effect of standard chemotherapy, or:

H_0: $S_{dstat} = S_{pbo}$

The alternative hypothesis is that the effect of dociparstat plus standard chemotherapy on OS and EFS does not equal the effect of standard chemotherapy, or:

H_A: $S_{dstat} \neq S_{pbo}$

9.2. Sample Size Determination

Approximately 1000 potential participants are expected to be screened to achieve a total of approximately 570 participants randomly assigned to study intervention.

Sample size calculations were based on the OS primary and EFS key secondary endpoints. Randomized Phase 2 data in the subset of participants matching our proposed Phase 3 population show an observed OS HR of 0.51 and control median OS of 16.1 months; however, these estimates are associated with substantial uncertainty given the small size of the Phase 2 study as well as actual and potential emerging post-induction and post-relapse therapies for patients with AML. To account for these factors, we assume a clinically-meaningful OS HR of 0.7 and a control median OS of 18 months; this corresponds with a dociparstat median OS of 25.7 months. Hence, assuming 24-month accrual, 24-month minimum follow-up time, and accounting for one formal interim analysis (see Section 9.5), the planned sample size will have >85% power to demonstrate a difference between treatment arms at a two-sided type I error rate of 4%. The target number of OS events is 308.

Similarly, we assume a clinically-meaningful EFS HR of 0.7, and a control median EFS of 10 months, 24-month accrual, and 24-month minimum follow-up. Hence, the planned sample size will have >85% power to demonstrate a difference between treatment arms at a two-sided type I error rate of 1%. Under the assumptions of 50% CR rates in both groups and no separation of the curves during the first 6 months, this is expected to result in 454 events.

9.3. Analysis Sets

The following analysis sets are defined:

Analysis Set	Description
Screened	All participants who sign the ICF.
Intent to Treat (ITT)	All participants who are randomized. Participants will be analyzed in the group to which they were randomized.
Safety	All participants who are randomized to and receive at least one dose of blinded dociparstat or placebo. Participants will be analyzed in the group corresponding to the first blinded dose of study intervention received.

Analysis Set	Description
Per protocol (PP)	All participants who are randomized to and receive at least one dose of blinded dociparstat or placebo, excluding those who have any significant inclusion/exclusion criteria violation or noncompliance that would be expected to impact the analysis of efficacy. Participants will be analyzed in the group corresponding to the first blinded dose of study intervention received.

The ITT analysis set will be used to summarize all efficacy endpoints. The PP analysis set will be determined prior to unblinding and will be used for supportive primary and key secondary efficacy analyses and possibly other selected endpoints to be defined in the Statistical Analysis Plan (SAP). The safety analysis set will be used for all safety and all other non-efficacy (e.g., medical history, medications, exposure) analyses.

9.4. Statistical Analyses

All analyses will be presented by randomized group (dociparstat, placebo), unless otherwise specified. The SAP will be finalized prior to the first interim analysis. It will include a more technical and detailed description of the statistical analyses described in this section, which is a summary of the planned analyses of the most important endpoints, including primary and key secondary endpoints.

9.4.1. Primary Endpoint

The primary OS inferential analysis will utilize the ITT analysis set and a log-rank test at two-sided alpha 0.04 stratified by baseline FLT3 status, cytogenetic risk, and age. Kaplan-Meier (KM) methods/plots and Cox models will be used. Log-rank p-values and hazard ratios with 95% CIs will be presented for each treatment comparison. Median failure times, KM estimates every 90 days, and corresponding 95% CIs will be presented for each group. Survival time will be measured from randomization. Participants who are not known to have died will be censored at the time they were last known to be alive. The final primary analysis will be conducted after approximately 308 death events have been observed.

9.4.2. Key Secondary Endpoint

The key secondary EFS endpoint will be tested using the same method as the primary endpoint at two-sided alpha 0.01. A participant with any bone marrow CR assessment between Days 22 and 42, inclusive, after start of induction or reinduction treatment will be considered an induction success; relapse and death events will be assessed following the last CR assessment during this time period. A participant with no CR assessments during this window will be considered an induction failure and imputed as such at randomization. Participants with induction success and no observed relapse or death events will be censored at the time they were last known to be alive. Maximum neutrophil and platelet counts within 7 days before or after the bone marrow draw will be used to determine count recovery. The key secondary analysis will be supplemented by a planned sensitivity analysis (not subject to alpha control), in which participants progressing to hematopoietic cell transplant will be censored at the time of transplant. The key secondary analysis will be conducted at the same time as the final primary OS analysis.

9.4.3. Other Secondary Endpoints

In the event that both the primary and key secondary analysis rejects the null hypothesis, the secondary analyses of $MRD_{neg,}$ time to platelet recovery, time to neutrophil recovery, and CR will be tested in a fixed sequential manner at two-sided alpha 0.05. If the primary analysis rejects the null hypothesis while the key secondary does not, these secondary analyses will be tested in a fixed sequential manner at two-sided alpha 0.04; similarly, if the key secondary analysis rejects the null hypothesis while the primary analysis does not, these secondary analyses will be tested in a fixed sequential manner at two-sided alpha 0.01. No other multiplicity adjustments will be made for secondary analyses.

Time-to-event secondary analyses will use the same methods used for the primary and key secondary analyses.

Dichotomous secondary efficacy analyses will be analyzed using a Cochran-Mantel-Haenszel test stratified by each of the stratification factors. Number of successes/failures and success/failure rates will be presented for each treatment arm. Cochran-Mantel-Haenszel p-values, estimated common odds ratios, and corresponding approximate 95% CIs will be presented for each comparison. The Breslow-Day test will be used to test the homogeneity of the odds ratios across the strata. Missing data will generally be imputed as failure unless specifically defined otherwise in the SAP.

Cumulative incidence of relapse will be analyzed with death as a competing risk adjusted for baseline strata, with corresponding cumulative incidence plots, Fine-Gray models, and cause-specific and sub distribution hazard ratios with corresponding 95% CIs.

OS, EFS, and MRD will be analyzed by various subgroups, including, but not limited to, each of the stratification factors, anthracycline use, sex, and race (each race contributing >10% to the study plus other races grouped). OS and relapse will be analyzed by number of consolidation cycles. Multivariate modelling to assess the impact of these factors on key endpoints will be considered and defined in the SAP.

9.4.4. Safety Analyses

All safety analyses will be presented using the safety analysis set. Inferential analyses will generally not be performed for safety endpoints unless specified in the SAP. Frequency and percentage will be presented for categorical variables. Sample size, mean, standard deviation, median, interquartile range, and range will be presented for continuous variables.

9.4.4.1. Adverse Events

Treatment-emergent AEs (TEAEs) are those that begin on or after the date of the first dose of study intervention and on or before 42 days after the start of the last cycle of study intervention.

Summaries (number and percent of participants) of TEAEs (by system organ class and preferred term) will be provided as follows:

- All
- Severe, life-threatening, and fatal

- Treatment-related
- Severe, life-threatening, and fatal treatment-related
- Serious
- Treatment-related serious
- Those leading to study intervention discontinuation
- Those leading to study intervention interruption
- Fatal

9.4.4.2. Laboratory Results

Descriptive statistics (N, mean, standard deviation, median, Q1, Q3, minimum, and maximum) will be provided for each continuous laboratory test as follows:

- Baseline values
- Values at each postbaseline analysis window (to be defined in the SAP)
- Change from baseline at each postbaseline analysis window

The minimum, maximum, and last postbaseline value / change from baseline will also be summarized. Missing data will not be imputed.

Laboratory tests will be descriptively analyzed by grade and analysis window using counts and percentages. The maximum and last postbaseline grade for each participant will also be summarized. Denominators will be the number of participants with a graded (or normal) test during the window. Laboratory tests with criteria for both increased and decreased levels will be analyzed for each direction (i.e., increased and decreased). This analysis will be generated twice to count (1) treatment-emergent increases in laboratory grades (i.e., only those above the baseline grade) and (2) any grade regardless of baseline.

9.4.4.3. Safety Subgroup Analyses

TEAEs Grade 3 and above, serious TEAEs, and treatment-emergent increases in laboratory grades will be summarized by age (<65, ≥65 years), race/ethnicity (separate categories for racial/ethnic groups contributing at least 10% of study enrollment plus “other”), sex (male vs female), and weight (tertiles). Other subgroups may be specified in the SAP.

9.4.5. Other Analyses

Other analyses, including but not limited to participant enrollment, analysis sets, demographics, baseline characteristics, prior and concomitant medications, study intervention usage, pharmacokinetics, and medical resource utilization will be specified in the SAP or other specific analysis plans.

9.5. Interim Analyses

Two interim analyses are planned.

The first interim analysis will be an early unblinded (only to the DMC) assessment of CR, CR with MRD_{neg}, and MRD_{neg}. This analysis will be reviewed by the DMC after 80 evaluable participants complete induction and reinduction (if applicable) assessments. Evaluable participants for this purpose are defined as those who either have a valid MRD result from the induction therapy recovery bone marrow (i.e., Day ~22 to 42), discontinue from induction therapy due to an AE or progressive disease, or die during induction therapy. The study will continue recruitment and enrollment while the interim analyses are being performed; a decision will be made as soon as practicable (targeted within 3 months) after the last participants' last assessments to be included in the analysis.

Three outcomes are possible from this analysis:

- The observed risk difference for CR is >30%, the observed risk difference for MRD_{neg} is >50%, or the combined total of observed risk differences for CR and CR with MRD_{neg} is >40%. The study will remain blinded and continue as planned.
- Observed risk differences for CR, MRD_{neg}, and CR with MRD_{neg} are all <5% The study will be unblinded to all parties and stopped.
- Criteria are not met for either of the preceding scenarios. The study will be unblinded to the sponsor, who, in consultation with the United States Food and Drug Administration, will determine whether to continue or stop the study. If the study continues, participants contributing to the interim assessment will not be used in subsequent inferential analyses and will be replaced. A summary of the data will be shared with investigators and ethics committees and publicly presented. Participants randomized after the interim cutoff and not contributing to the assessment will remain blinded and will contribute to subsequent inferential analyses.

The second interim analysis will be an unblinded (only to the DMC) efficacy assessment. It will be completed after approximately 250 OS events are observed. The O'Brien-Fleming alpha spending function will be used to control the familywise type I error rate. Therefore, the interim OS test will be performed at the 0.0196 nominal two-sided alpha level, and the final OS test will be performed at the 0.0342 nominal two-sided alpha level. On the condition that the study proceeds beyond the first interim analysis, this approach is expected to yield >68% power at the time of this second interim analysis for the primary OS endpoint under the sample size assumptions noted. The key secondary EFS endpoint will also be tested at this time, with the alpha level determined based on the total number of observed EFS events using an alpha spending function that maps to the O'Brien-Fleming boundary. In the event that this interim analysis is successful for either endpoint, the database will be unblinded to the sponsor to facilitate regulatory submissions. Regardless of conclusions from the second interim analysis, participants will continue to be followed as prescribed, with individual group assignments remaining blinded at the site level.

Additional details of the planned interim analyses will be included in the SAP and DMC charter (or associated documents).

9.6. Data Monitoring Committee

Study data will be periodically reviewed during the study by an independent, unblinded DMC at prespecified timepoints:

- After ~80 evaluable participants complete induction and reinduction (if applicable) assessments (safety data and interim analysis for efficacy).
- After approximately 200, 300, and 400 participants have been randomized and completed at least 4 months of follow-up (safety data).
- After approximately 250 OS events are observed (interim analysis for efficacy).

The DMC will also be provided with real-time, expedited safety reports. The DMC chair may schedule ad hoc safety review meetings at any time during the study as deemed appropriate.

Details of the DMC membership and review procedures will be outlined in a separate charter.

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11. APPENDICES: SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

11.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The investigator will submit the protocol, protocol amendments, ICF, and other relevant documents (e.g., advertisements) to an IRB/IEC for review and approval by the IRB/IEC before the study is initiated. Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will also be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Oversight of the conduct of the study at the site and adherence to requirements of US regulations (21 CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- Notify the IRB/IEC of protocol deviations, unanticipated problems, and serious breaches of GCP according to local guidelines and maintain this documentation in the sites' study file.

11.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with enough accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after study completion.

11.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and/or legally authorized representative and will answer all questions regarding the study.
- Participants must be informed that their participation is voluntary.
- Participants or their legally authorized representative (as defined by local regulations) will be required to sign a statement of informed consent that meets the requirements of US regulations (21 CFR Part 50), local regulations, ICH guidelines, and the IRB/IEC. In some situations, verbal or remote consent may be permissible.
- The authorized person obtaining the informed consent must also sign the ICF.
- The medical record must include the date informed consent was obtained and a statement that consent was obtained before the participant was enrolled in the study.
- When the ICF is amended, the investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF document(s) by the IRB/IEC prior to use. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- The investigator must maintain the original and any amended signed and dated ICFs. A copy of each signed ICF must be provided to the participant and/or the participant's legally authorized representative.

The ICF shall contain authorization for the use and disclosure of the participant's protected health information in connection with the study. The authorization shall include at a minimum a clear description of the following: the duration of the authorization, the right of access to the information (or any suspension thereof during the course of the study), type of information to be used/disclosed in the study, names or classes of parties that may use or disclose information, purpose of the use/disclosure, extent of the right to revoke the authorization, extent to which participation in the study is conditioned on signing the authorization, and potential for redisclosure of protected health information.

The ICF will address the optional biobanking of bone marrow and blood samples for exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate in exploratory research and may withdraw their consent at any time and for any reason during the storage period.

If a prescreening ICF is used for screening assessments (e.g., bone marrow analyses) to determine eligibility before a participant consents to the full study, the participant will be clearly informed that the purpose for prescreening is to identify participants to enroll in the full study.

11.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will only contain the identifier; any information that would make the participant identifiable (e.g., name) will not be transferred. The investigator will

keep an enrollment and identification log that contains a record of the personal identification data linked to each participant's study identification number.

Encoded participant data will be transferred to the sponsor (located in the US) and will be stored indefinitely. Encoded data will be used by the sponsor for safety reporting, research and development, regulatory purposes, and marketing of dociparstat; encoded data may also be shared with other companies or individuals for research purposes.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with US Health Insurance Portability and Accountability Act (HIPAA) requirements (where applicable) and/or national data protection/privacy laws (outside of the USA), including without limitation the General Data Protection Regulation (GDPR) 2016/679 (in the European Union). The participant will be required to give consent for their data to be used as described in the informed consent document.

The participant must be informed about the level of disclosure and that his/her medical records may be examined by clinical quality assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

11.1.5. Data Quality Assurance

All observations relating to the study will be recorded by site personnel in source documents. In addition, an eCRF must be completed for every participant entered into the study. The eCRF must be completed according to the eCRF completion guidelines. After each participant has completed the study, the investigator must review and electronically sign the eCRFs indicating that (s)he has reviewed the completed eCRFs and pertinent clinical data for the participant and that, to the best of his/her knowledge, all data recorded in the eCRFs accurately reflects the participant's performance in the study.

Quality controls are incorporated into project management activities conducted by Chimerix (or its designee), including the monitoring and verification of clinical and safety data.

The investigator must permit study-related monitoring, audits, IRB/IEC reviews, and regulatory agency inspections and provide direct access to source data documents. Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements. Remote monitoring will be considered on a site-by-site basis and conducted following procedures outlined in the appropriate study-specific plans (e.g., monitoring plan), and in accordance with current available guidance regarding regulatory authority opinion on remote monitoring.

Essential documents pertaining to the conduct of the study should be retained for the following time period:

- At least 2 years after approval of the last marketing application.

  OR

- At least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

These documents should be retained for a longer period (e.g., 15 years or more), however, if required by applicable local or country-specific regulatory requirements or by an agreement with Chimerix. It is the responsibility of Chimerix to inform the investigator/institution as to when these documents no longer need to be retained. If it becomes necessary for Chimerix or any regulatory authority to review any documentation relating to the study, the investigator must permit access to such records.

11.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of data collected. Source documents are filed at the investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. Participants' medical records must be available for inspection. The investigator may need to request medical records from other providers in order to have all relevant data available.

11.1.7. Study and Site Start and Closure

The study start date is the date on which the first randomized participant signed the ICF (i.e., first participant, first visit).

The clinical study will be open for recruitment of participants when the first site has completed site initiation, has study intervention onsite, and has been notified by the sponsor (or designee).

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further development of the study intervention.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, IECs/IRBs, regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform participants at their study center and should ensure appropriate therapy and/or follow-up.

11.1.8. Dissemination of Clinical Study Data

Results of the study will be posted on the relevant clinical study registration websites (e.g., clinicaltrials.gov and the European Union clinical trials register). Results of the study will

also be submitted for publication in a peer-reviewed scientific journal, unless the study is terminated prematurely and does not yield sufficient data for a publication.

11.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

11.2. Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

11.2.1. Definition of an AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition or is fatal.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

11.2.2. Definition of an SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study).

SAEs

An SAE is defined as any untoward medical occurrence that, at any dose:

1. **Results in death**
2. **Is life-threatening**

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

3. **Requires inpatient hospitalization or prolongation of existing hospitalization**

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.
- Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is an SAE.
- When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Exceptions:

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. Hospitalization for protocol therapy administration.
- Hospitalization for diagnostic investigations (e.g., scans, endoscopy, sampling for laboratory tests, bone marrow sampling) that are not related to an AE.
- Hospitalization for technical, practical, or social reasons, in absence of an AE.
- Hospitalization for a procedure that was planned prior to study participation (i.e., before consent or randomization).
- Hospitalization for administration of blood or platelet transfusion as routine treatment of the studied indication.

- However, hospitalization or prolonged hospitalization for complications of administration of study intervention, diagnostic investigations, planned procedures, or administration of blood or platelet transfusion remains reportable as an SAE.

4. **Results in persistent disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

5. **Is a congenital anomaly/birth defect**

SAEs
6. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

11.2.3. Recording and Follow-Up of AEs, SAEs, and AEs of Special Interest

AEs, SAEs, and AEs of Special Interest (AEOSI)
Recording
• When an AE/SAE/AEOSI occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE/AEOSI information in the eCRF/data collection tool, as appropriate. • The investigator will promptly (preferably within 24 hours) respond to all queries related to an SAE/AEOSI. • It is not acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the AE/SAE/AEOSI eCRF/data collection tool. • There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant's study number, will be redacted on the copies of the medical records before submission. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE/AEOSI.
Assessment of Intensity
The investigator will assess the intensity for each AE/SAE/AEOSI reported during the study and assign an intensity/severity grade based on the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]). Note: An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is of severe intensity.
Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/AEOSI. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship.

AEs, SAEs, and AEs of Special Interest (AEOSI)

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the investigator's brochure for dociparstat and the product information for cytarabine, daunorubicin, and idarubicin (as applicable).
- For each AE/SAE/AEOSI, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/AEOSI and has provided an assessment of causality.
- There may be situations in which an SAE/AEOSI has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always assess causality for every event before initial transmission of the SAE/AEOSI data to the sponsor.
- The investigator may change his/her opinion of causality after follow-up information is available and send an SAE/AEOSI follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE/SAE/AEOSI as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study (at any time from randomization through long-term follow-up), the investigator will provide the date of death and a determination of cause of death (including any supporting information, such as death certificate, pathology or autopsy information, as applicable).
- The investigator will submit any updated SAE/AEOSI data to the sponsor within 24 hours of receipt of the information.

11.2.4. Reporting of SAEs

SAE Reporting to the Sponsor

- The primary mechanism for reporting an SAE to the sponsor is the eCRF/data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool to report the event within 24 hours.
- Contact details for SAE reporting are included in the study reference manual.

11.3. Appendix 3: Contraceptive Guidance and Pregnancy Reporting

11.3.1. Definitions

Woman of childbearing potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered a woman of childbearing potential

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study eligibility.

   Note: Documentation can come from site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle-stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, confirm with more than one follicle stimulating hormone measurement.
   - Females on hormone replacement therapy and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their hormone therapy during the study. Otherwise, they must discontinue hormone therapy to allow confirmation of postmenopausal status before study enrollment.

11.3.2. Contraception Guidance

Males must

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.

OR

- Agree to use a male condom with spermicide when having sexual intercourse with a woman of childbearing potential throughout the study and for at least 90 days after the last dose of study intervention or chemotherapy. The participants should also be advised of the benefit for his female partner to use a highly-effective method of contraception as a condom may break or leak.

Females must:

- Be of nonchildbearing potential.

OR

- Agree to use a highly-effective method of contraception throughout the study and for at least 90 days after the last dose of study intervention or chemotherapy.

Contraceptive Methods Allowed During the Study include the Following:

Highly-Effective Methods That Have Low User Dependency

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
  Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.

Highly-Effective Methods That Are User Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  - oral
  - intravaginal
  - transdermal
  - injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation
  - oral
  - injectable
- Sexual abstinence
  Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Notes:
Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
Highly-effective methods have a failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

Contraceptive Methods that are <u>NOT ACCEPTABLE</u> During the Study include the Following:

- Periodic abstinence (calendar, symptothermal, post-ovulation methods).
- Withdrawal (coitus interruptus).
- Spermicides alone.
- Lactational amenorrhea method.
- Use of both male condom and female condom together, because of the risk of failure with friction.

11.3.3. Collection of Pregnancy Information

Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the pregnancy outcome. The investigator will collect follow-up information on the participant and neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

11.4. Appendix 4: Genetic Risk Categories

Risk Category	Cytogenetic findings	Molecular genetic findings
Favorable	– t(8;21)(q22;q22.1) – inv(16)(p13.1q22) or t(16;16)(p13.1;q22)	– RUNX1-RUNX1T1 – CBFB-MYH11 – NPM1 mutated without FLT3-ITD or NPM1 mutated with FLT3-ITD^{low} – Biallelic mutated CEBPA
Intermediate	– Normal karyotype – t(9;11)(p21.3;q23.3) (takes precedence over rare, concurrent adverse-risk gene mutations) – Cytogenetic abnormalities not classified as favorable or adverse	– NPM1 mutated and FLT3-ITD^{high} – NPM1 wild-type without FLT3-ITD or with FLT3-ITD^{low} (without adverse-risk genetics) – MLLT3-KMT2A
Adverse	– t(6;9)(p23;q34.1) – t(v;11q23.3) – t(9;22)(q34.1;q11.2) – inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2) – –5 or del(5q); –7; –17/abn(17p) – Complex karyotype – Monosomal karyotype	– DEK-NUP214 – KMT2A rearranged – BCR-ABL1 – GATA2, MECOM(EVI1) – NPM1 wild-type and FLT3-ITD^{high} – Mutated TP53 – Mutated RUNX1 – Mutated ASXL1 (Not adverse if co-occur with favorable-risk AML subtype)

Source: Döhner 2017

Low, low allelic ratio (<0.5); high, high allelic ratio (≥0.5); semiquantitative assessment of FLT3-ITD allelic ratio is determined as ratio of the area under the curve "FLT3-ITD" divided by area under the curve "FLT3-wild type"

Monosomal karyotype=Single monosomy (excluding loss of x or y) with at least 1 additional monosomy or structural chromosome abnormality (excluding core-binding factor AML).

Complex karyotype=Three or more unrelated chromosome abnormalities in the absence of 1 of the World Health Organization-designated recurring translocations or inversions.

11.5. Appendix 5: ECOG Performance Status (and Associated Karnofsky Grades)

ECOG Grade	ECOG Status Description	Associated Karnofsky Grades	Karnofsky Status Description
0	Fully active, able to carry on all predisease performance without restriction.	100	Normal, no complaints.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, (e.g., light housework, office work).	90	Able to carry on normal activities. Minor signs or symptoms of disease.
		80	Normal activity with effort.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	70	Care for self. Unable to carry on normal activity or to do active work.
		60	Requires occasional assistance, but able to care for most needs.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	50	Requires considerable assistance and frequent medical care.
		40	Disabled. Requires special care and assistance.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	30	Severely disabled. Hospitalization indicated though death not imminent.
		20	Very sick. Hospitalization necessary. Active supportive treatment necessary.
		10	Moribund
5	Dead	0	Dead

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

11.6. Appendix 6: Drugs Known to Prolong the QT Interval

The following drugs (list is not exhaustive) are known to prolong the QT-interval:

- amiodarone
- astemizole
- azithromycin
- bepridil
- chloroquine
- chlorpromazine
- ciprofloxacin
- cisapride
- citalopram
- clarithromycin
- disopyramide
- dofetilide
- domperidone
- droperidol
- erythromycin
- escitalopram
- flecainide
- fluconazole
- granisetron
- halofantrine
- haloperidol
- ibutilide
- levomethadyl
- mesoridazine
- methadone
- moxifloxacin
- ondansetron
- pentamidine
- pimozide
- posaconazole
- probucol
- procainamide
- quinidine
- sevoflurane
- sotalol
- sparfloxacin
- terfenadine
- thioridazine
- voriconazole

11.7. Appendix 7: Definitions of Terms

Term	Definition for this Study
Chemotherapy	Cytarabine + anthracycline (either daunorubicin or idarubicin) induction/reinduction therapy, followed by cytarabine consolidation therapy, when indicated
Consolidation therapy	Inclusive of all consolidation cycles (i.e., 1, 2, 3, or 4 cycles) received under this protocol.
Induction therapy	Inclusive of the initial induction cycle and a reinduction cycle when indicated
Recovery bone marrow	The bone marrow aspirate collected on ~Day 22 to 42 of a treatment cycle. Generally collected after (at the time of) hematologic count recovery; if counts have not recovered, the sample will still be collected on ~Day 36 to 42 of the cycle.
Study intervention	Dociparstat or placebo
Treatment cycle	Consists of the administration of therapy (i.e., chemotherapy with cytarabine ± anthracycline plus blinded study intervention) and all scheduled assessments to evaluate the response to treatment, including bone marrow and hematologic recovery.
Treatment period for the study	The time from randomization through the final treatment cycle.

Response / Outcome		Definition (Based on ELN 2017 Recommendations)
Response	Complete remission with complete hematologic recovery (CR)	Bone marrow blasts <5%, absence of circulating blasts and blasts with Auer rods, absence of extramedullary disease, ANC >1.0 x 10^9/L (1000/μL), and platelet count >100 x 10^9/L (100,000/μL).
	CR with incomplete hematologic recovery (CRi)	All CR criteria (bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease), except for residual neutropenia (≤1.0 x 10^9/L [1000/μL]) or thrombocytopenia (≤100 x 10^9/L [100,000/μL]). [Note: Participants with both residual neutropenia and residual thrombocytopenia are not considered to have achieved CRi.]
	CR with partial hematologic recovery (CRh)	Bone marrow blasts <5%; no evidence of disease, and partial recovery of peripheral blood counts (ANC >0.5 x 10^9/L [500/μL] and platelets >50 x 10^9/L [50,000/μL], but the count recovery criteria for CR are not met).
	Measurable residual disease negative (MRD_{neg})	Negative (undetectable) MRD in bone marrow, as measured by MFC (0.1% detection limit).

Failure	Treatment failure (induction failure)	Failure to achieve CR within 42 days of the start of induction therapy (or start of reinduction therapy when applicable).
Relapse	Relapse (hematologic)	After achievement of CR/CRi, bone marrow blasts ≥5%, reappearance of blasts in the blood, or development of extramedullary disease.
	Cumulative incidence of relapse	Measured from the date of randomization until the date of relapse. Participants not known to have relapsed will be censored on the date of last follow-up contact.
Outcome Measure	Overall survival (OS)	Measured from the date of randomization to date of death from any cause.
	Event-free survival	Measured from the date of randomization to treatment failure, relapse, or death from any cause, whichever occurs first.
	Relapse-free survival (RFS)	Measured from the date of randomization to date of relapse or death from any cause.
	Time to recovery	Time to recovery of neutrophil count is measured as time from date of randomization until the first day the ANC is >500/μL and is >1000/μL following induction or reinduction (if indicated). Time to transfusion-independent platelet recovery is measured as time from date of randomization until the first day the platelet count recovers to >20,000/μL, >50,000/μL, and >100,000/μL, without a platelet transfusion in the preceding 5 days following induction or reinduction (if indicated).

11.8. Appendix 8: Abbreviations

7+3	7-day infusion of cytarabine and 3 days of idarubicin or daunorubicin as AML induction or reinduction therapy
5+2	5-day infusion of cytarabine and 2 days of idarubicin or daunorubicin as AML reinduction therapy
AE	adverse event
AEOSI	adverse event of special interest
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BM	bone marrow
CI	confidence interval
Cmax	maximum observed concentration
CR	complete remission with complete hematologic recovery
CRh	complete remission with at least partial hematologic recovery
CRi	complete remission with incomplete hematologic recovery
CTCAE	Common Terminology Criteria for Adverse Events
CX-01	dociparstat sodium, 2-O, 3-O desulfated heparin
CXCL12	chemokine SDF-1, and abbreviation for stromal cell derived factor-1
CXCR4	receptor for the chemokine SDF-1
DMC	data monitoring committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF / CRF	electronic case report form / case report form
EFS	event-free survival
eGFR	estimated glomerular filtration rate
ELN	European LeukemiaNet
FISH	fluorescence in situ hybridization
FLT3	FMS-like tyrosine kinase 3
GCP	good clinical practice
HCT	hematopoietic stem cell transplant

HMGB1	high mobility group box protein 1
HR	hazard ratio
ICF	informed consent form
ICH	International Council for Harmonisation
IRT	interactive response technology
ITD	internal tandem duplication
ITT	intent to treat
IV	intravenous
MFC	multiparameter (multicolor) flow cytometry
MRD	measurable (minimal) residual disease
MRD_{neg}	measurable (minimal) residual disease negative
ODSH	(previously-used abbreviation for) 2-O, 3-O desulfated heparin
OS	overall survival
PK	pharmacokinetic
RFS	relapse-free survival
SAE	serious adverse event
SAP	statistical analysis plan
t½	terminal elimination half-life
TEAE	treatment-emergent adverse event
TKD	tyrosine kinase domain
Tmax	time to maximum observed concentration
ULN	upper limit of normal

11.9. Appendix 9: Protocol Amendment Summary of Changes

Rationale for protocol Amendment 1: Broaden the eligibility criteria to permit enrollment of additional participants in the study.

Deleted text is shown as ~~strikethrough~~ and new text is shown in **bold**. The synopsis has been updated to align with changes in the protocol body. The amendment includes additional changes for clarity that have not been included in Table 10.

Table 10: Changes Included in Amendment 1

Section(s)	Change	Rationale
1.2: Schedule of Activities, Table 1; 6.1: Study Intervention(s) Administered, Table 5	~~FLT3-positive~~ Participants may receive cytarabine 200 mg/m^2/day **according to local practices (e.g., for FLT3-positive participants)**	Some investigators indicated 200 mg/m^2/day is their standard cytarabine dose for all patients.
3: Objectives and Endpoints	**Proportion of participants who receive any HCT (allogeneic or autologous) during the study.**	New endpoint to account for participants who may receive an autologous HCT if a suitable match is not available.
4: Study Design	**Of the first 80 participants enrolled, the number of participants age 18 to 59 years with intermediate risk genetic risk will be limited to 20.**	To ensure adequate representation from the original planned population in order to assess outcomes from the first 80 evaluable subjects and inform subsequent investigation.
4: Study Design; 5: Study Population; 5.1: Inclusion 2b	… ≥18 years old with ~~adverse genetic risk or ≥60 years old with either~~ intermediate or adverse genetic risk… 2b. Intermediate genetic risk ~~(≥60 years only)~~…	Inclusion criteria modified to permit enrollment of participants 18 to 59 years of age with intermediate genetic risk to broaden study population.
5.1: Inclusion 3	Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 ~~if ≤79 years of age; ECOG status of 0 or 1 if ≥80 years of age~~.	Criterion modified to broaden study population.
5.2: Exclusion 2	~~AML with a history of antecedent myelodysplasia that has been previously-treated (e.g., with a hypomethylating agent).~~ ~~Note: Myelodysplasia that has not been previously treated is permitted.~~	Criterion removed to broaden study population.
5.2: Exclusion 3	~~Therapy-related AML after prior radiotherapy or chemotherapy for another cancer or disorder.~~	Criterion removed to broaden study population.

Section(s)	Change	Rationale
5.2: Exclusion 15	QTc ~~>450~~ **>480** msec ~~for a male, >470 msec for a female, or >480 msec if underlying bundle branch block~~.	Criterion modified to broaden study population.
5.2: Exclusion 19	**History of allergy or hypersensitivity to heparin, pork, or any excipients in the dociparstat formulation.**	Criterion added to as a potential risk for participants.
5.2: Exclusion 20	**Any other condition, including abnormal laboratory values, that, in the judgment of the investigator, could put the participant at increased risk or interfere with the conduct or planned analyses of the study.**	Criterion added to cover other potential risks not specified as individual exclusion criteria.
6.2.2: Handling, Storage, and Accountability	~~Dociparstat should be stored at controlled room temperature (i.e., 15°C to 25°C [59°F to 77°F]), with excursions permitted to 30°C (86°F); protect from freezing~~. **[Note: the labeled storage conditions are dependent on the manufactured drug product batch/lot.]**	Storage conditions will be changing when the next batch of drug product is manufactured and released.
7.1: Interruption of Study Intervention	Infusion of study intervention may be resumed once QTc is ~~<450~~ **<480** msec. Following resumption of infusion, ECGs are to be checked daily until the participant has had 3 consecutive (daily) tracings with QTc ~~<450~~ **<480** msec, after which follow-up ECGs will be as per institutional standard of care.	Criterion modified to align with change in Exclusion 15.
8.2.2: Response Criteria and Outcome Measures; Appendix 7	*Definition of CRh* … partial recovery of peripheral blood counts (ANC >0.5 x 10^9/L [500/µL] and platelets >50 x 10^9/L [50,000/µL], **but the count recovery criteria for CR are not met**).	Clarification.
8.3.3: Electrocardiograms	At subsequent time points, a single ECG tracing will be obtained, with a repeat tracing to confirm QTc intervals ~~>450~~ **>480** msec.	Criterion modified to align with changes in Exclusion 15 and Section 7.1.

Rationale for protocol Amendment 2: Revert back to the original standardized cytarabine dosing to reduce variability. Deleted text is shown as ~~strikethrough~~ and new text is shown in **bold**. The synopsis has been updated to align with changes in the protocol body.

Table 11: Changes Included in Amendment 2

Section(s)	Change	Rationale
1.2: Schedule of Activities, Table 1; 6.1: Study Intervention(s) Administered, Table 5	**FLT3-positive** Participants may receive cytarabine 200 mg/m^2/day ~~according to local practices (e.g., for FLT3-positive participants)~~	Revert to the original standardized cytarabine dosing to reduce variability.

SPONSOR'S SIGNATURE PAGE

Protocol Title: A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of dociparstat sodium in combination with standard chemotherapy for the treatment of newly diagnosed acute myeloid leukemia

Protocol Number: CMX-DS-003

Protocol Date: 19 August 2021 (Amendment 2)

This protocol has been approved by Chimerix, Inc.

The following signature documents this approval.

Allen Melemed

Digitally signed by Allen Melemed
DN: cn=Allen Melemed, o=Chimerix, ou=Chief Medical Officer, email=amelemed@chimerix.com, c=US
Date: 2021.08.20 11:14:31 -04'00'

Allen Melemed, MD
Chief Medical Officer

INVESTIGATOR AGREEMENT

Protocol Title: A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of dociparstat sodium in combination with standard chemotherapy for the treatment of newly diagnosed acute myeloid leukemia

Protocol Number: CMX-DS-003

Protocol Date: 19 August 2021 (Amendment 2)

I have received and read this protocol, the Investigator Brochure, and all other study-related information provided to me.

I agree to conduct the study in accordance with the protocol, International Council for Harmonisation Good Clinical Practice (ICH GCP) guidelines, and all applicable local laws and regulations pertaining to the conduct of clinical studies.

I will ensure that all subinvestigators and other staff members involved with the conduct of the study read and understand all aspects of this protocol.

I agree to maintain the confidentiality of all information received or developed in connection with this protocol. All rights of publication of the results reside with Chimerix, Inc., unless made in a separate agreement.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date